UNOFFICIAL TRANSCRIPT*
WASHINGTON STATE PHARMACY AND THERAPEUTICS COMMITTEE MEETING

September 21, 2005
Radisson Hotel SeaTac
9:00am – 2:30pm

Committee Attendance:
Angelo Ballasiotes, Pharm D.
Robert Bray, M.D.
Carol Cordy, M.D, (Vice Chair)
Alvin Goo, Pharm D.
Jason Iltz, Pharm D.
Janet Kelly, Pharm D.
T. Vyn Reese, M.D.
Patti Varley, ARNP

A quorum was shown for all Pharmacy & Therapeutics Committee motions, 2nd's, and votes.

9:00 a.m. - Committee came to order.

WELCOME & INTRODUCTIONS

Carol Cordy, M.D.: How's this? Give us about five minutes to get everybody seated. We thought we'd be ready but we're not.

Man: Okay. Why...when you...you let me know and when…

Carol Cordy, M.D.: The vice chair, the P&T Committee…

Man: Carol, pretend like this is a trumpet; you have to have it right in front of your mouth.

Carol Cordy, M.D.: Right in front of me. Okay. Should we start by just going around and introducing…

Man: Yes.

Carol Cordy, M.D.: ourselves? Go ahead.

Erika Clayton: Erika Clayton, Health Care Authority.

Duane Thurman: And I'm Duane Thurman, Health Care Authority.

Donna Marshall, Pharm D.: Donna Marshall, Health Care Authority.

Elizabeth James: Elizabeth James, Uniform Medical Plan.

Nancy Fisher, M.D.: I'm Nancy Fisher, Medical Director, Health Care Authority.

Jeff Graham, M.D.: Jeff Graham, Health Care Authority.

Jason Iltz, Pharm D.: Jason Iltz, P&T Committee member.

Robert Bray, M.D.: Robert Bray, family physician, Spokane, P&T Committee.

T. Vyn Reese, M.D.: Vyn Reese, internal medicine, geriatrics, Seattle.

Angelo Ballasiotes, Pharm D.: Angelo Ballasiotes, Yakima, Mental Health.

Patti Varley, ARNP: Patty Varley, child and adolescence psyche nurse practitioner, Children's Hospital, P&T Committee.

Janet Kelly, Pharm D.: Janet Kelly, member of the P&T.

Jamie Mai: Jamie Mai, Labor and Industry.

Nicole Nguyen, Pharm D.: Nicole Nguyen, MAA or HRSA.

Siri Childs, Pharm D.: Siri Childs, pharmacist for HRSA.

Jeff Thompson, M.D.: Jeff Thompson, HRSA.

Jeff Graham, M.D.: Carol, can I make a few announcements here?

Carol Cordy, M.D.: Sure.

Jeff Graham, M.D.: I've been told to speak clearly into the microphone, and also always identify yourselves. When we review the transcripts we really can't tell who was speaking so we want you to be sure and identify yourself. And also, by speaking clearly into the microphone, the folks on the telephone can hear you clearly. So I think we're ready to go.

Peter Glassman, M.D.: Okay. I couldn't hear everybody's introductions, so I may need names if you...when you speak to me. I may not uh, I may not have heard your name before. So if you don't mind introducing yourself if you have questions at the end...that would be...that would be helpful. My name is Peter Glassman. I'm an internist by training and I'm also involved with Rand's Evidence-based Practice Center. And I will be presenting the drug class review of the newer antiplatelets agents today. One quick caveat, as I went through this Janet um...my colleague, Janet, put together the slides and one of the things I've noticed, we will have to we will have to um, fix is that the slide...some of the slide numbers seem to be repetitive, so I do apologize for that. But I will try to describe the slide as we go through.

I will try to highlight...you know, the slide presentation by its very nature, of course, over the phone is a little harder than usual. And also it will be an abbreviated version of what is obviously a much longer document. I will try to highlight, using the slides, some of the findings and then we can talk about some of these issues, if you like, afterwards. Um, the...as you're probably already aware, the search strategy...this is slide No. 2, the search strategy is fairly similar to...or similar to what we have done before, or what the groups have done before using various registries and searches to get relevant articles. I won't go over all...obviously over all those details. Data collection analysis, again, was similar to prior work in Oregon. One difference that we've been doing...I don't know if the others have been doing, is we do an analysis of adverse events. A compiled analysis. Again, I won't...a pulled analysis. I won't go into all the details. It's not that important for the import...for the uh, for the current presentation.

Inclusion data is listed on the next slide. I think you're already familiar with that. We will go over some of the key questions in the second.

Uh, the medications. Important too to look at. The three that are currently available, the newer antiplatelets, that's the Aggrenox, or extended release Dipyridamole, Clopidogrel, Plavix, and Ticlid or Ticlopidine. The inclusion criteria, part of the questions were all cause and cardiovascular mortality, various cardiovascular vents and invasive procedures. And safety outcomes are on the next slide. Overall adverse events; withdrawal, withdrawal serious adverse events as well as others.

So the key questions addressed in this uh, review uh, do the newer antiplatelet agents differ in efficacy in the adult patients with ACS, coronary intervention procedures, stroke or TIA, or peripheral vascular disease. And second, do the newer antiplatelet agents differ in safety for the same population. And are there specific subpopulations, third question, which may have more or less effect and less...more or less fewer adverse events for the agents under discussion.

The following uh, slide, labeled as Key Question No. 1 Results, gives you sort of a very brief overview of what was available in terms of the literature. We're obviously going to...I'm obviously going to highlight some of the more important aspects today. An on the next slide it talks about the comparative efficacy of the newer antiplatelet agents for ACS, and of particular interest to us is the cure trial. Now, I'm not sure, does...did people want me to go over the basics of the CURE trial? Or...well, let me…

Woman: Yes.

Peter Glassman, M.D.: I...let's just... for everybody...obviously the CURE was a trial that involved Clopidogrel plus aspirin vs. placebo plus aspirin. So in essence it was aspirin plus Clopidogrel vs. aspirin alone. And looking at various aspects of ACS. It was an...Obviously in a very large group of patients, we have it listed for you on the slide. In terms of its outcome at 12 months, there was a

nonsignificant different in mortality, but the 2 primary composite end points, which are listed on the slide, uh, showed benefit, and that is death from cardiovascular causes, not fatal MI. Stroke showed a reduction in the Clopidogrel and aspirin group. And when you looked at those endpoints plus refractory ischemia, those obviously a reduction as well when listed on the slide. The definition of the terms he uses right at the bottom of the slide, RR relative risk, ARR or RRR is relative risk reduction, ARR is absolute risk reduction and NNT is numbers needed to treat.

On the...continuing to look at the CURE trial, the MI rates for Clopidogrel vs. placebo were lower...or Clopidogrel plus aspirin vs. aspirin plus placebo was 5.2...you can see that number there, 5.2% vs. 6.7%. And the stroke risk was non-significantly reduced. It was actually very small. The numbers were very small as well. So...and that is in the manuscript. And also, in terms of invasive vascular procedures, there were fewer coronary...excuse me, nonsignificant difference in coronary revascularization procedure rates.

Looking at PCI, percutaneous interventions, this gives a listing of the trials themselves, and again we'll focus on a few. Now it's important to understand that when looking at the comparative issues across these agents, many of you are already aware that some of these agents are not going to be used for some of these indications. For example, we don't expect to see Aggrenox being tested for coronary disease. So it's...in the terms of comparativeness, one has to look at the comparator against other standards. There is some overlap, but in general just keep in mind that obviously these are used for a variety of indications that may not overlap in certain instances. So there are no trials, for example, with Aggrenox and that's listed on this slide. So, really when we're looking at PCI what we're really looking at is three agents. Aspirin is the standard and then Ticlopidine and Clopidogrel.

So the Classics trial was a head-to-head trial of Clopidogrel and aspirin and then Ticlid and aspirin. Looking at that the all cause...see, the all cause mortality...I'm holding the phone in one hand, flicking slides with the other and turning papers with my third arm. So you'll have to excuse me as I as I leaf through here a little bit. The 30-day major adverse clinical events, so the classical was one of its secondary outcomes. Uh, um, was one of its...sorry, was one of its secondary outcomes. And um, cardiovascular events were not reported and evasive vascular procedures were not reported.

Um, looking at PCICURE...I'm sorry, these are just listing of the artic...listing of the um, listing of the various studies. PCI CURE and Credo, again this just gives you a very brief encapsulation of the study itself. PCI CURE and Credo Obviously those are much greater detail in the manuscript for you. And I'm looking at the next slide, which is PCI efficacy of Clopidogrel. Cardiovascular death at 30 days and death at 1 year was not significant between the two groups. But the composite end point of cardiovascular death and MI before PCI was, and that shows a difference of 8.8% in favor of Clopidogrel over aspirin alone, and the relative risk is given there. In credo the death from any cause at one year for pretreatment versus no treatment had showed no significant difference.

And the next slide continues on the efficacy of Clopidogrel. The PCI cure, MI within 30 days, showed a benefit in favor of Clopidogrel. Group...or the Clopidogrel group, I should say. 2.1% vs. 3.8%. And the relative risk and the confidence intervals are given for you as well as the number needed for you to treat. MI at one year, well as again, in favor of the Clopidogrel group. And the numbers there are 4.5% vs. 6.4%, with a relative risk of .71, and again the confidence at 95% confidence intervals are listed for you along with the number needed to treat. Just to keep in mind, stroke was not an outcome eval...stroke alone was not an outcome evaluated in the PCI cure trial. Or stroke was not an outcome, I should say. Credo, the composite endpoint of death, myocardial infarction and stroke, was in favor of the Clopidogrel group, 8.5% vs. 11.5%, relative risk reduction...or relative risk, excuse me, of .73 with its confidence intervals around it.

The next slide is the invasive vascular procedure. Failures I sh... PCI cure showed urgent re...a nonsignificant different difference in urgent revascularization in 30 days between the groups. But the composite endpoint of nonfatal MI urgent TVR and cardiovascular death at 30 days was in favor of the Clopidogrel group 4.5% vs. 6.4% with the data listed on the slide. Any revascularization from a PCI up to one year was in favor of Clopidogrel...Clopidogrel group. Again, the confidence interval was there for you. And finally the composite endpoint of cardiovascular death MI or any revascularization was in favor of the Clopidogrel group. Okay. Next slide.

In Credo the composite death rate myocardial infarction or PDR at 28 days showed 8.3% in the no pretreatment group with no Clopidogrel vs. 6.8 pretreatment, but that was a nonsignificant difference.

So in summary...summary slide, Clopidogrel and aspirin were superior to aspirin alone in uh, for acute...um, excuse me, acute coronary syndrome. Mean duration of follow up was nine months, and in reducing their combined end point of myocardial infarction stroke, cardiovascular death as well as refractory ischemia.

For PCI the long-term administration...the relatively long-term administration of Clopidogrel plus aspirin after PCI was associated with lower rate of the composite endpoint and a benefit was seen in reducing the rate of cardiovascular events in patients undergoing PCI with Clopidogrel and aspirin. And the pretreatment loading dose of Clopidogrel more...or six hours or more prior to PCI reduced the relative risk by the numbers stated on the slide.

Uh, for key question No. 1 in terms of stroke or TIA, there are no head-to-head trials. But there are some good studies available to us and on the new slide it lists the major studies. ESPS 2, which has looked at aspirin and long-acting Dipyridamole, LATS, which is fairly recent, show...looked at Clopidogrel vs. Clopidogrel and aspirin, and TAS, which looked at Ticlid vs. aspirin, Ticlopidine plus aspirin. Let me just pull some more paperwork here.

On the next slide, on the comparative efficacy of new antiplatelet agents for stroke. In ESPS 2 the combined product of extended release Dipyridamole and aspirin reduced the risk of strokes by the relative risks data on the slide. And it was 24%...the actual numbers are 9.5% vs. 12.5% for the all strokes. And nonfatal strokes at 24 months. Again, reduction the numbers are 8.3% vs. 11.3%. Um, in match, which was the study with Clopidogrel and Clopidogrel and aspirin, there wasn't a difference in the outcomes at 18 months.

Continuing on to the next slide, in cardiovascular events for stroke and MI, there was no difference at 5 years for the stated endpoints. When you look at nonfatal and fatal stroke, you had a nominal...well, it was just above .05, point .06 for combined nonfatal and fatal stroke with a risk reduction that's listed on that slide, 16%. And in CARAS, a tough study...we included it, but it's a tough study to really get a handle on, but what we're really looking at is using a transcranial Doppler to look at signals that might indicate throwing off of emboli. So...micro-emboli. So it was a...we included it, but one has to take into consideration that this is not really an outcome study but rather an imaging or a study done by imaging and it's unclear what kind of clinical relevance it has at this point, it was so short. Anyway, it's listed for you what the study is.

The next slide, Invasive Vascular Procedures, it wasn't an endpoint study, an ESPS 2, TAS, or CARAS, and in match there was no difference in the group for composite primary endpoint including rehospitalization for acute ischemic events.

So in summary, ESPS 2 showed that the combination of extended release Dipyridamole and aspirin reduced the incidence of strokes and ischemic and...Cerebrovascular ischemic events in general and death compared to aspirin alone. But Match studies showed that aspirin plus Clopidogrel was no more effective than Clopidogrel alone in the major vascular event rates in high risk patients who in they had...the enrollees were those who had suffered a...recently suffered an ischemic stroke or TIA. And in TAS, Ticlopidine 250 mg twice a day was somewhat more effective than aspirin in reducing the risk of death from any cause of the risk of nonfatal stroke in patients with a recent TIA minor stroke. In CARAS, which is this very short study, Clopidogrel plus aspirin was more effective than aspirin alone in reducing the proportion of micro-embolic signals, and the numbers are listed there for you. Again, it's unclear what that means clinically. All right.

Continue on to the next key questions in peripheral vascular disease. Looking at efficacy of Clopidogrel. Uh, Clopidogrel, if you recall, Capri was done in a group of mixed vascular disease patients. So it was those who had recent ischemic stroke, MI or established peripheral arterial disease... peripheral vascular disease. And it included over 19,000 patients. In terms of all cause cardiovascular mortality, death from any cause at 36 months was not significant. It was 5.9 vs. 6%. And vascular death at 36 months was also not significant. It was 4.0 vs. 3.7%. However, the combined end point of stroke, myocardial infarction, vascular death, at that endpoint 36 months, did show a small difference and that was .51% absolution difference with a P value of .043 and a relative risk. That relative risk is incorrect. It should be 90...relative risk was 91%, not 19%, with a 95% confidence interval around that. We'll get that corrected.

Looking at the next slide, the sub analysis on the acute myocardial infarction at 36 month showed a benefit in favor of Clopidogrel 4.2% vs. 5.04%, relative risk reduction of 19...r...roughly 19%. It's important to note that stroke as an independent endpoint was not evaluated. On invasive cardiovascular procedures it really should read "cluster endpoint of amputation or ischemic stroke, MI or vascular death." But anyway, not significant difference.

Looking at the next slide. Summary of efficacy. Um, I...the way I would phrase this is a little difference. I would say Clopidogrel was slightly better than aspirin in reducing the combined risk...or combined endpoint in patients with mixed vascular diseases of the ones stated earlier. Who are treated for the duration of the study. We are going to talk a little bit later, just at the very end...we can get into the various subgroups.

Looking at adverse events. I think the key thing on this slide is the key question two, overall adverse events of Thienopyridine. Looking at some of the data from the other meta analysis, the major difference, these are fairly minor, but you can see the event rates between Clopidogrel and Ticlid for...and vs. aspirin, for diarrhea, skin rash and indigestion.

The next slide…

T. Vyn Reese, M.D.: I had a question. This is Dr. Reese.

Peter Glassman, M.D.: Yeah.

T. Vyn Reese, M.D.: You didn't mention hemologic side effects from Ticlopidine.

Peter Glassman, M.D.: We're gonna get...we'll get there.

T. Vyn Reese, M.D.: Okay.

Peter Glassman, M.D.: Yeah, we're gonna get there. This is overall adverse event rates, and then you...you're talking about...I can't hear you very well, but I think you...you're talking about um, uh, the neutropenia?

T. Vyn Reese, M.D.: Right.

Peter Glassman, M.D.: Yeah. We're gonna we're gonna...we'll get there in oh, a few slides. Uh, key things out here is just uh, skin disorders in terms of Clopidogrel showed a safety profile superior to that of Ticlopidine overall 4.6% vs. 9.1% and this is in a head-to-head classics trial. Skin disorders .7 vs. 2.6%. GI disorders 1.3 to 2.6%. In the Capri, for example, the overall instance of GI events was 27.1% with the Clopidogrel and 29.8% with aspirin and that was significant. In cure GI events, abdominal pain, dyspepsia, gastritis, constipation were higher with aspirin than Clopidogrel, 12.5% vs. 11%. And in the cure trial rash and other skin disorders were more common with Clopidogrel than compared with aspirin, 4.0 vs. 3.5% with a P value of .05. Or less than or equal to .05. Okay.

In the Cochran meta analysis, just to point out that Clopidogrel was associated with a 30% more rash and diarrhea compared to aspirin whereas Ticlopidine increased the rate of rash and diarrhea by more than twofold over aspirin.

The next slide just goes in, again, more of overall adverse events. Headache was more commonly seen. Most adverse events in the ESPS 2 trial included headache, dizziness and GI symptoms, including diarrhea, which occurred more frequently in patients treated with Dipyridamole extended release. Withdrawals, the next slide, headache and diarrhea occurred most frequently resulting in higher withdrawal rates, not surprisingly in the extended release Dipyridamole, based on the...not surprising, based on what I just said in the last slide. And a rash and diarrhea were the most common reasons to stop Ticlopidine, more so than with Clopidogrel. Uh, just to give you some more on that.

At 30 days, for example, adverse even...GI adverse events accounted for 56% of treatment sensation in the two extended release Dipyridamole groups and 38% in the non extended release Dipyridamole groups. And in the head-to-head PCI trials that compared Clopidogrel with the Ticlid...Ticlopidine , excuse me, rash was the most frequent reason for discontinuing the medications. More so for Ticlid...Ticlopidine than Clopidogrel.

In the Classics trial, which you'll recall was Clopidogrel and Ticlopidine, Clopidogrel was better tolerated than Ticlopidine for the primary endpoint. Major peripheral bleeding complications; neutropenia or thrombocytopenia or early discontinuation of the study drug and skin rashes, primarily rash were the most frequent reason for discontinuing therapy with instances of 2.6% for Ticlopidine and .5% for Clopidogrel users.

Finally, in the TAS study, which we remember is Ticlopidine vs. aspirin, discontinuation due to adverse events, primarily a...diarrhea and rash occurred in 14.5% of the patients on Ticlopidine and 6.1% in those taking aspirin. Next slide.

In CURE, the major bleeding rates was 3.7% vs. 2.7%. Um, and that is for...the first is for aspirin plus Clopidogrel and the second is for aspirin with a relative risk of 1.4. I wonder if that's...you know, that doesn't sound right to me. That relative risk. I'll have to check that. That looks more like an odds ratio. But, anyway. Bear with me on that. It was statistically significant. The 3.7% vs. 2.7% was significant. Major bleeding was significantly higher with increased aspirin doses. Now this is a post hoc analysis show that major bleeding was significantly high with increasing aspirin doses. And minor bleeding was significant with Clopidogrel plus aspirin vs. aspirin alone, number being on the slide 5.1 vs. 2.4%.

In the match study you can see the bleeding rates. And I think this is the key to the match study is that we didn't find, or we didn't see a benefit of Clopidogrel plus aspirin on important cerebrovascular ischemic rates. We did see changes in the bleeding rates, however, and they're listed for you on that slide. I think of particular note is the life threatening and the bleeding, of course. The next slide.

Going back to the question on neutropenia and severe neutropenia, which is defined at the very base of the slide for you. You can see that in this instance uh, Ticlopidine had a higher rate of the Thienopyridine. between Ticlopidine and Clopidogrel. This is based on the meta analysis. And in severe neutropenia, again, the different rate.

In summary, the comparative safety is at least based on the adverse event profiles we can say that. Clopidogrel alone seems to be safer than its sister drug Tic...Ticlopidine. And looks to be about as safe as aspirin. Or is as safe as aspirin. Um, in general, at least the data suggests that Clopidogrel is the drug that should be used in favor of Ticlopidine based on the adverse hematological effects, particularly, obviously, neutropenia. And I would say rather than...and a third point, rather than should be dosed, I would say that the post hoc data suggests that the lower aspirin doses seem to have the more safer profile when used in combination with a Thienopyridine. But again that's a post hoc analysis. Hold on one sec.

Looking at the uh, uh, the evidence of efficacy and safety among various populations, really overall within the studies in terms of age, racial groups and gender, for the amount of data that was presented and we found, really we're not finding any major differences between those groups for the various studies that we had data. So, for example, subset analysis in cure and ESPS 2 showed no difference in the benefits when looking at age. I won't go through the entire slide, it just basically summarizes. I think when you go to the next slide, looking at the evidence of comparative efficacy and safety of the newer antiplatelet agents, there are some subgroups that may have had a different benefit, for example, in cure diabetics had a lower incidence of the first primary outcome. When looked at specifically diabetics had a lower incidence of the first primary outcome. And I think it's in general ESPS 2 showed that patients with ischemic heart disease, for example, or diabetes, also had good results from...or showed a benefit with Aggrenox, or long...excuse me, the long-acting Dipyridamole and aspirin. And in Capri, when looked in the subgroup populations, one particular subgroup population showed a particular beneficial outcome and that is the patients with peripheral arterial disease where when looking at the primary outcome the difference was 3.7% vs. 4.86%. Relative risk reduction was around 23% with a P value of roughly speaking .028, I think it was. Yeah.

And that's basically the summary of the document. Obviously I'll be happy to take whatever questions you may have.

Carol Cordy, M.D.: Thank you, Peter. This is Carol Cordy. Were there any stakeholders who wanted to speak?

Peter Glassman, M.D.: I couldn't...were there any stakeholder what?

Carol Cordy, M.D.: Were there any stakeholders who wanted to speak? Do you know?

Man: I think it would be good to ask questions of Dr. Glassman first and then have the stakeholders speak. Is that all right, Carol?

Carol Cordy, M.D.: Sure, that's fine.

Jeff Graham, M.D.: So…

Carol Cordy, M.D.: Any questions?

Jeff Graham, M.D.: the members have some questions.

T. Vyn Reese, M.D.: Dr. Glassman, this is Dr. Reese. And after reading the reports and your review, based on the evidence presented, it looks like Clopidogrel is...has definitely has indications for acute coronary syndromes and post angioplasty and stents. And it looks like Aggrenox has definite indications for TIA and stroke prevention. Is that fair based on what you've presented to us?

Peter Glassman, M.D.: Yeah, I'm sorry. I'm having I'm having a hard time hearing you. What I heard was that Clopidogrel has an indication for ACS and post stent. And that Aggrenox or long-acting Dipyridamole and aspirin have the indication for or would be used for patients at uh...who have uh, cerebrovascular ischemia. Is that is that correct?

T. Vyn Reese, M.D.: That's correct. And Ticlopidine is a drug with too many side effects at this point to be in the mix uh, based on what you've said.

Peter Glassman, M.D.: Yeah, I don't...I think it's fair to say that Ticlopidine use has generally been supplanted by Clopidogrel in our various communities. I don't expect to see any future studies, obvious...for obvious reasons on Ticlopidine vs. this...so we're not really playing, if you will, Ticlopidine against Clopidogrel. And we're really not pitting Aggre...uh, extended release Dipyridamole and aspirin against Clopidogrel, except in the one area where it becomes a little bit more confusing as to what to do and that is in terms of cerebrovascular events. But you're...I think your summary is right on.

T. Vyn Reese, M.D.: Thank you.

Carol Cordy, M.D.: Any other questions or comments. Okay, we have two stakeholders. First of all Dr. Kyle Downey.

[end Side A]

[Side B]

Man: …to not know the lingo. A stakeholder is…what describes a stakeholder? What defines a stakeholder?

Man: A stakeholder is described as anyone who may have interest in this drug class and for us it's generally pharmaceutical manufacturers and occasionally we might have advocacy groups or individuals who might come to give testimony. I would ask you to stay on the line for this. It will take probably about a total of 10 minutes and…because they may bring up some questions that we're unable to- that we may want to ask you specially.

Man: Oh sure, no problem.

Kyle Downey: Good morning chair person and members of the committee. My name is Kyle Downey. I'm a regional medical liaison with Sanofi Aventis. I'm here to make public comments on the drug Plavix. Plavix is a medication as we've seen that has demonstrated efficacy in coronary, cerebral and peripheral circulation and it is certainly a medication that will benefit many patients in the Washington Medicaid population.

It's important to think about atherosclerosis as an ongoing inflammatory process that affects the coronary, cerebral and peripheral circulation. In the Capri trial, which was outlined of 20,000 patients, approximately 26% of those patients had ischemic vascular events in two or more vascular beds demonstrating the generalized nature of atherothrombosis. Outlined were two double blind control trials where the Capri study and the Cure study…in the Capri study Clopidogrel showed an overall 8% relative risk reduction over aspirin and in the Cure study Clopidogrel plus aspirin showed a reduced relative risk reduction of 20% in cardiovascular death, non-fatal MI and stroke. The ACCAJ Class I recommendations added Clopidogrel to their recommendations for antithrombotic events. In the non-conventional approach Clopidogrel should be added to aspirin as soon as possible on admission and afterwards administered for at least one month and up to nine months. In the PCI patient population Clopidogrel should be started and continued again for at least one month and up to nine months for patients who are not at high risk of bleeding. And long-term therapy the combination of aspirin and Clopidogrel is recommended for nine months after UA…unstable angina and non-ST segment elevation MI.

Also outlined were the PCI-Cure and CREDO trials. I would actually like to touch base on two more recent clinical trials, which looked at Clopidigrels use in the ST segment elevation MI of patient population in conjunction with [inaudible] therapy. The CLARITY patient population was a worldwide trial and showed a 36% relative risk reduction in the composite end points of TIMI flow, death and MI. And the commit study, which comprised 46,000 patients showed a 7% relative risk reduction in death along as well as a 9% relative risk reduction in death, reinfarction or stroke.

Moving on to the cost effectiveness of the medication. As we know the annual cost of cardiovascular disease is estimated to be over $300 billion and there have been cost effective analysis showing adding Clopidogrel to aspirin is favorable, cost effective when compared to other cardiovascular therapies. And in patients undergoing PCI Clopidogrel is both effective and cost effective and dominant in the ACS patient population.

In conclusion Plavix itself gives patients proven protection from thrombotic events. Benefits were seen early and maintained in long-term therapy for up to a year in the Cure trial. Life-threatening bleeding was non-significant and major bleeding rates were dose dependent based upon aspirin. And the efficacy of Plavix was independent of the dose of aspirin.

One last thing I would like to comment on was in the two recent trials of Clarity and Commit, major bleeding was not statistically significantly increased with Clopidogrel added onto aspirin in contemporary therapy. I would like to open it to any questions.

Carol Cordy, M.D.: Any questions for Dr. Downey? Thank you. Dr. Susan Wood.

Susan Wood, M.D.: Good morning. My name is Dr. Susan Wood and I'm a national medical scientist with Goehringer Ingelheim Pharmaceuticals. I would like to commend the Oregon group for their report, but there are one or two points that we wanted to bring out. One of them being…concerning the CAPRIE trial and how the peripheral arterial disease patients were highlighted. There were over 6,000 patients in that trial who had had stroke and also over 6,000 patients who had previous MI. A predefining test for heterogeneity was positive indicating that each patient population did not respond similarly to Clopidogrel treatment. For stroke patients and MI patients there was no significant difference in efficacy between Clopidogrel and aspirin arms for their primary end point. However, there was a 28.3% relative risk reduction for stroke, MI and vascular death in the pad patients.

The Match trial demonstrated that in high-risk stroke and TIA patients the combination of Clopidogrel and aspirin is no more effective at preventing ischemic stroke, MI, vascular death or rehospitalization than Clopidogrel alone. However, the combination of therapy did significantly increase bleeding.

In the ESPS II trial, which was a stroke patient trial, we did not see an increase in bleeding when you combined extended release Dipyridamole and aspirin over aspirin alone.

The extended release Dipyridamole plus aspirin that you find in Aggrenox contains Dipyridamole pellets that have an extended release coating and a core tartaric acid for increased absorption. In individuals with low gastric acid the extended release Dipyridamole in Aggrenox provides 50% higher bioavailability than immediate release Dipyridamole. And this is, of course, important in patients who are elderly and those who are taking acid blockers. And Aggrenox prescribing information contains a cautionary statement mandated by the FDA that Aggrenox is not interchangeable with the individual components of aspirin and Persantine.

One last point that I wanted to make was that there is a head-to-head trial ongoing of extended release Dipyridamole plus aspirin versus Clopidogrel in stroke patients. This is called the Profess trial and it is designed to investigate the superiority of Aggrenox versus Plavix in secondary prevention and it's also investigating the effects of Telmisartan and ARB on stroke. Thank you.

Carol Cordy, M.D.: Are there any questions of Dr. Wood? Thank you.

Jeff Graham, M.D.: This is Jeff Graham. Are there further questions for Dr. Glassman? If not, he could probably depart the meeting. Is that fine? So Dr. Glassman, we appreciate very much your being available for this presentation and I think that we will be able to proceed now and you could go on with your other work.

Dr. Glassman: Oh, thank you very much. I do appreciate it and I wish you all luck in your deliberations. Thank you. Take care.

Carol Cordy, M.D.: This is Carol Cordy. Is there any discussions in the group? Do we want to proceed with a motion? Does anybody want to take this on and make a motion?

T. Vyn Reese, M.D.: This is Dr. Reese and I'll work on this. I actually think two motions need to be made. I think that both of the drugs that have been reviewed need to be added, but for slightly different indications based on the evidence we've heard this morning. First one, after considering the evidence of safety, efficacy and special populations for the treatment of acute coronary syndromes and percutaneous coronary interventions, I move that Plavix is safe and effective. No single anti platelet agent associated with fewer adverse effects in special populations. Plavix cannot be subject to therapeutic interchange in the Washington preferred drug list for the treatment of acute coronary syndromes and percutaneous coronary…why don't we skip that one…percutaneous coronary intervention.

Jeff Graham, M.D.: This is Jeff Graham. Would you mind if we used the generic name in that? Clopidogrel?

T. Vyn Reese, M.D.: You can just substitute Clopidogrel for Plavix.

Carol Cordy, M.D.: This is Dr. Cordy. Can I just …I heard some word about efficacious rather than effective. I move that Clopidogrel is safe and efficacious. Just a change in wording.

T. Vyn Reese, M.D.: Yeah, should be is instead of are.

Carol Cordy, M.D.: Right.

Donna Marshall, Pharm D.: Do you want efficacious instead of effective? Is that what you are saying?

Carol Cordy, M.D.: That's what I'm saying.

Jeff Thompson, M.D.: Carol, this is Jeff Thompson. Are you directing Medicaid then to use this language as part of its expedited prior authorization? Because when you're on a preferred drug without expedited prior authorization then it is indicated in all FDA indications. And there are no restrictions.

Carol Cordy, M.D.: I guess I'm not clear.

Jeff Thompson, M.D.: I believe that all of these drugs, and correct me if I'm wrong, the FDA indications cross over both coronary vascular events as well as cerebral vascular events.

T. Vyn Reese, M.D.: They don't.

Jeff Thompson, M.D.: Okay. I just wanted to make sure.

Siri Childs, Pharm D.: This is Siri Childs with HRSA. We currently have these drugs on EPA for the appropriate indication and if we would make these preferred without EPA then it would be wide openly used without any guidance set on.

Alvin Goo, Pharm D.: Hi, this is Alvin. What is the current prior auth for Clopidogrel and Aggrenox?

Siri Childs, Pharm D.: Right now they are exactly what the FDA indications are.

T. Vyn Reese, M.D.: This is Dr. Reese. So if…in order to order one of them you would have to basically write out what the indication was to order it? Is that how it would work now?

Siri Childs, Pharm D.: If this committee would like to use the evidence based review to direct the use of the different agents according to, you know, specific indications then we would have to have EPA to guide that rather than just have it open coverage.

T. Vyn Reese, M.D.: I'm still confused by this. Let's say somebody is coming out of the hospital and they have just had an angioplasty and stent placed and the cardiologist wants to order Plavix for them. How does that happen? I mean when they are discharged the medications are going home on Plavix or Clopidogrel. How does the state handle that?

Siri Childs, Pharm D.: As long as it is for post stent replacement it is covered and the patient communicates that to the pharmacist. When the pharmacist is inputting the order he puts in a code and it automatically goes through for that indication.

T. Vyn Reese, M.D.: So you don't have to call and get prior auth for something like that?

Siri Childs, Pharm D.: Right. Mm hm.

T. Vyn Reese, M.D.: Okay. And so basically what you're concerned about is if we open this up to be on a non-preferred basis or not prior…without prior review then it could be…Plavix could be prescribed for gout or for shingles or for anything else. Is that what your concern is? In other words you're concerned about is it being prescribed for other indications that are not FDA approved. And you have a safe and effective way of getting it to the patients without having an administrative block being placed on…

Siri Childs, Pharm D.: It's been on EPA since it's come onto the market.

T. Vyn Reese, M.D.: Okay. So do we need to…I mean the question is do we need to go through this exercise then if you've already got it on a system like that? Do we want to add it to the formulary of all or do we want to continue on that? Where are we with that? It makes it sort of a…the formulary question mute.

Siri Childs, Pharm D.: If you decide that the evidence shows that one agent is better for a specific indication we can re-write our expedited criteria to guide the use according to that.

T. Vyn Reese, M.D.: Well clearly this drug is superior for those indications than the others. Okay? So there is no question that this drug should be used for those indications. Now for CNS indications it's more murky.

Jeff Thompson, M.D.: Again, just to be clear, I mean when you put something on the preferred drug list you comment on…this is Jeff Thompson. You comment on interchange and then by putting it on the preferred drug list as a preferred drug then DAW applies regardless of the indication for the endorsing status provider and then for a non-endorsing they would have to call up if it was non-preferred. If it was preferred they could write for whatever indication. So just…I mean just so we're clear preferred status is directly related to interchange, DAW and endorsing status. When you put any kind of indications about efficacy or special populations typically what we do is we draw that into expedited prior authorization. It does not require a phone call, but it directs that they have to have a certain clinical indication, please, please, scouts honor, make sure that this clinical indication applies.

Siri Childs, Pharm D.: So you can have a preferred drug for a specific indication or indications, but it still would be a preferred drug for that indication. It just would require EPA in the HRSA program.

Janet Kelly, Pharm D.: This is Janet Kelly. I'm just wondering if we can…I think we are all sort of trying to say the same thing and we're having problems getting the English to work for us. I'm wondering if what we could do is to say, "After considering the evidence of safety, efficacy, skip the special populations for the treatment of acute coronary syndromes, PCI, and peripheral- what's the

other one- CNS one," I move that Clopidogrel and Dipyridamole extended release in aspirin are efficacious. And then we can specify…pull out that the Clopidogrel is for the acute coronary syndromes and PCI in that way. Is that going to make us get where we want to be? I don't know. I'm having a hard time with this English.

Carol Cordy, M.D.: Carol Cordy, here. It sounds like the problem is being on the preferred drug list or still being prior auth…on the prior authorization list. Right? Or expedited prior authorization.

Siri Childs, Pharm D.: I don't see that as a problem. I think that you can call it a preferred drug for those indications and in order for us to implement that we would put it on EPA for those indications. It would be preferred for those indications.

Carol Cordy, M.D.: So it would still be on the expedited prior authorization?

T. Vyn Reese, M.D.: So we don't want to have this motion made? Is that right? This is Dr. Reese. So we don't want to make this motion at all or do we?

Siri Childs, Pharm D.: I think that you could make this motion as long as you specify the indications per each drug.

Robert Bray, M.D.: This is Bob Bray. So it sounds like what I'm hearing is that the original motion by Dr. Reese is fine and that because there are indications in there even if it isn't on the preferred drug list, it would remain on EPA because of the needing to control its use for those indications. So that was fine. Correct?

Jeff Thompson, M.D.: This is Jeff Thompson. I apologize for the confusion, but again 6088 applies to endorsing, DAW and interchange. You've addressed the interchange, but an endorsing provider, correct me if I'm wrong Duane, an endorsing provider writing DAW then can write it for whatever indication they want. We just have a stop in there that the pharmacist would say, "Maybe I want to call the physician if it's not for this indication. They don't have to call us, but there might be an interchange between the pharmacist and the physician.

Jeff Graham, M.D.: This is Jeff Graham. Clarification – I think we have done this before. We've done this in the Statin class for Pravachol and just by putting these indications in this motion has worked just fine. And also for, I believe, the ACE inhibitors one of them and also…I can't remember the other one.

Jeff Thompson, M.D.: We're just trying to be very careful about what we do and very clear about, you know, there is EPA criteria so that if an endorsing provider writing DAW for a non-EPA indication he or she may get a call from a pharmacist saying, "Did you know that the P&T committee said it was for this indication alone?"

Carol Cordy, M.D.: On a practical level, if I'm writing under DAW and I put for acute coronary syndrome I won't get that call.

Jeff Thompson, M.D.: Right. But if you did it for gout the pharmacist may call you up.

Carol Cordy, M.D.: They may or they should? Shouldn't they?

Donna Marshall, Pharm D.: Jeff, I have a question real quick. This is Donna Marshall. The Clopidogrel is actually looks like also FDA approved for peripheral vascular disease. So is that…was that purposely excluded or is that…

[inaudible]

Donna Marshall, Pharm D.: Yeah, it's ACS, stroke, TIA and peripheral vascular disease. So there might be concerns if…

T. Vyn Reese, M.D.: The evidence is less robust for these other indications, but it clearly it's got very strong indications of these two and it's FDA approved for the others. So it would have to be…we would have to include peripheral vascular disease and recent stroke. I think if we're going to go by FDA approval as we said we were.

Donna Marshall, Pharm D.: So do I need to insert them?

T. Vyn Reese, M.D.: Right.

Alvin Goo, Pharm D.: Hi, this is Alvin. I guess I'm a little bit…this is where I guess it gets a little bit sticky is that in secondary prevention of stroke both the Match and the CAPRIE trial showed minimal or no difference when adding Clopidogrel with aspirin. So

right now if…I just question does Clopidogrel have a role based on the results of the CAPRIE and the Match? If we go forward what we're doing it does. And I think that is where I'm having a little bit difficulty in how to word that.

Carol Cordy, M.D.: I question, too. Are we…where does it come in that we have to add whatever is FDA approved? Do we have to add those just because they are FDA approved?

Donna Marshall, Pharm D.: You don't have to, but what Jeff Thompson was saying is that the drugs would be approved for the FDA indications. So the way you have it now is that they would only be approved for the acute coronary syndrome or the percutaneous coronary…

Carol Cordy, M.D.: That was because that is what the evidence shows.

Donna Marshall, Pharm D.: Correct.

Jeff Thompson, M.D.: This is Jeff Thompson again. Let me just correct…not approved. It would just be that if there were some question…a pharmacist under EPA may or may not call the physician as it relates to your instruction. They don't have to call MAA or HRSA, but the more restrictive you make this under EPA or the more restrictive you make this there may be an interaction with the pharmacist. And again it gets confusing because what we're doing is we're talking about a preferred drug list and we're talking about expedited prior auth and then we're also sort of getting into the clinical guideline field where you're trying to direct care based on the efficacy of randomized product.

T. Vyn Reese, M.D.: This is Dr. Reese. I'm just going to quote. The evidence is there it's just not as robust as the others. Okay? It just says, "Clopidogrel is slightly better than aspirin in reducing the combined risk of ischemic stroke, MI and vascular death in patients with symptomatic peripheral arterial disease were treated for a mean of 1.91 years." Very slightly positive, but it was positive and so I don't think we can include that. It's just not as good as the others…as the evidence for the other indication. So I think we're stuck putting it in for those two.

Nicole Nguyen, Pharm D.: This is Nicole. I just wanted to clarify like how we have had EPA with preferred drugs in the past with Altace and Pravachol, but basically that criteria works if they are a non-endorser and they have that indication the pharmacist would use the EPA code and it would go through. If it was a non-endorsing and they didn't have the indication then they would maybe call the doctor or have the, you know, have to call on it. But if you're endorsing and you write for it with DAW it will override…it will go through. It still…I just want to clarify that part. But if you don't put DAW, you know, then it would probably hit for the EPA and that indication. The only exception to that is the NSAIDS where we didn't let the endorsers override the GI history because that was a safety issue.

Carol Cordy, M.D.: But if you write DAW it would override even if I'm prescribing this for gout?

Woman: Yep.

Jeff Thompson, M.D.: This is Jeff Thompson. That is part of the preferred drug list that the physician gets a total bye with the preferred drug or a non-preferred drug under DAW regardless of the indications.

Carol Cordy, M.D.: So we're trying to keep this on the expedited prior authorization list or…

Patti Varley, ARNP: This is Patti Varley. I just want to be clear that is true across the board. We're not just talking about it in this example.

Man: Right.

Woman: Exactly.

Siri Childs, Pharm D.: This is Siri Childs again and I would encourage you to do what you believe the evidence says regardless of the FDA labeling. We do have to observe FDA labeling, but if there is evidence that shows that one is better I think that you would want the patient to have the benefit of that knowledge and if you want to guide therapy you can specifically tell us how to write the EPA criteria and I wouldn't…I don't think you should be trapped by the FDA labeling.

T. Vyn Reese, M.D.: The FDA labeling because there was evidence that was presented that that was the case. The FDA doesn't label something as indicated if there is no evidence. Usually the FDA has a reason for having it, you know, indicated for a condition. So I think we're in relatively safe ground. Sometimes the evidence is fairly weak and I think in this case it is, but they do have a reason.

Carol Cordy, M.D.: It seems like we need to decide whether we want to include the…whether it is weak evidence or no evidence of the…reducing the risk of ischemic stroke, MI and vascular death. Maybe we need to decide among the group whether we want to include those or just leave it with the acute coronary syndrome and the percutaneous coronary intervention. I mean you are saying we can do it how we feel the evidence leads us and then…the expedited prior authorization folks will have to do whatever they generally do with that. So is there any discussion on what we want to include that's up here in red? Do we want to include all of those indications? Or just stick with the original indications that Dr. Reese mentioned? I guess its kind of do we want to go with the FDA or go with the evidence?

Alvin Goo, Pharm D.: This is Alvin again. I think the evidence is pretty strong for ACS and PCI. Again, I don't know what to do with the secondary prevention data based on the Match or the CAPRIE. So my recommendation would be to keep the ACS and the PCI indication up there. I think that needs more discussion.

Robert Bray, M.D.: This is Bob Bray. I agree with Alvin.

T. Vyn Reese, M.D.: This is Dr. Reese. I think that you're right, but it's going to cause a lot of problems. I can see this causing lots of trouble. I know a lot of vascular surgeons are prescribing it for peripheral vascular disease and it's going to be difficult. That's why I broadened the indication the more I thought about it, even though the evidence is very weak.

Donna Marshall, Pharm D.: Dr. Reese, this is Donna Marshall. I have a question. Originally you said that you were going to have two motions. Was your intent to address peripheral vascular disease in the stroke in another motion?

T. Vyn Reese, M.D.: Yeah, stroke and TIA is for Aggrenox basically.

Donna Marshall, Pharm D.: Okay. So you were going to.

T. Vyn Reese, M.D.: That's the other motion. I wanted to go through this motion first and have it act in this one drug, but the indications are definitely not the same for the two drugs.

Donna Marshall, Pharm D.: Right. So I'm just going to say…

T. Vyn Reese, M.D.: One is truly a CNS drug and one is probably mainly cardiac with maybe some CNS and peripheral vascular thrown in. So it's…they're not exactly…the evidence isn't the same for both drugs for the same indications.

Donna Marshall, Pharm D.: So do we keep it or not?

T. Vyn Reese, M.D.: I understand what you're saying. I agree, but there are a lot of problems with that.

Man: And I agree with that. [unclear]. It's going to cause a lot of problems.

Carol Cordy, M.D.: Well, we don't have a second yet. As the motion stands is there a second?

Jason Iltz, Pharm D.: This is Jason. I think I would tend to agree with Alvin and Dr. Bray in that we really need to look at, safety aside, we need to look at if they are efficacious and if they are significantly more efficacious than standard therapies that are available. And so I think that is very clear for ACS, as well as for PCI. But I don't see the data as being clear in the other areas where there is an alternative and it's available over the counter and readily available. I think in guiding therapy it makes sense that the majority would benefit from those two indications and realize that just because they aren't on there if someone fails the other therapy they could certainly get that. This is really a first line type, you know, statement in saying that these are what's considered first line for these and if you need it for something else show us the evidence and it will be approved.

Janet Kelly, Pharm D.: This is Janet Kelly. I'm having a hard time following all of this and I think when we get to the stroke and TIA, and maybe you guys can just help me get this right in my mind, but what I'm seeing is there is a trial that looks at Clopidogrel and then the combination of Clopidogrel and aspirin and what they are saying is a combination of Clopidogrel and aspirin is not beneficial. I follow that. But where are we getting the information that…where's the combination between Clopidogrel compared to aspirin. I didn't see that? Did I miss it? Where…that's what we need to know. And I don't know if it's just that, you know, the presentation if I missed that piece somewhere, but I'm not finding that and that's what I really need.

T. Vyn Reese, M.D.: That was in the CAPRIE trial. It's combined in points, stroke, MI, vascular death at 36 months. It was aspirin versus Clopidogrel alone.

Man: They called it actually placebo didn't they?

T. Vyn Reese, M.D.: It's a placebo aspirin and the placebo…

Man: [inaudible]

T. Vyn Reese, M.D.: It was definitely aspirin versus Clopidogrel. So there is no question about it and it was slightly more efficacious in those multiple end points, which are all sort of a catch all.

Janet Kelly, Pharm D.: So where in this presentation…I still don't see it.

T. Vyn Reese, M.D.: Summary of evidence of Clopidogrel for peripheral vascular disease, which is…it's weak.

Man: It's on page 4 at the top, I believe.

T. Vyn Reese, M.D.: It's also on page 11.

Man: Slide number 10.

Janet Kelly, Pharm D.: My understanding is that isn't an acute coronary syndrome. Where's the stroke, TIA data?

T. Vyn Reese, M.D.: It's on page 10 and 11.

Janet Kelly, Pharm D.: 10 and 11.

T. Vyn Reese, M.D.: It's under peripheral vascular disease. At the bottom of the page it's the CAPRIE trial with the placebos for each aspirin and Clopidogrel.

Janet Kelly, Pharm D.: Here we are talking about peripheral vascular disease again.

T. Vyn Reese, M.D.: Right.

Janet Kelly, Pharm D.: Not stroke and TIA.

T. Vyn Reese, M.D.: That was stroke, MI and vascular death. It's a catch all. And it was barely significant.

Janet Kelly, Pharm D.: Yeah.

T. Vyn Reese, M.D.: If I don't get a second then I can modify my motion if that is what the committee wants and just eliminate the other indications—peripheral vascular disease, PCI stays, percutaneous coronary intervention stays and acute coronary syndrome. And those are the only two that stay. That was my original motion.

Carol Cordy, M.D.: Is there a second?

Robert Bray, M.D.: Second, Dr. Bray.

Carol Cordy, M.D.: Thank you. Any more discussion?

Woman: Can we just go over what the motion actually says now?

Carol Cordy, M.D.: Okay. After considering the evidence of safety, efficacy and special populations for the treatment of acute coronary syndrome and percutaneous coronary intervention I move that Clopidogrel is safe and efficacious. No single antiplatelets is associated with fewer adverse events in special populations. Clopidogrel cannot be subject to therapeutic interchange in the Washington preferred drug list for the treatment of ACS and PCI.

T. Vyn Reese, M.D.: Should it be antiplatelets drug? Antiplatelets sounds really kind of awkward.

Woman: You can make the "a" small.

Man: The "a" under antiplatelet. Yeah.

Carol Cordy, M.D.: Is there anyone needing more clarification? All in favor, "I".

Group: I.

Carol Cordy, M.D.: Opposed? Okay. Now, did you want to make a second motion?

Man: Unless somebody else does. Alvin, why don't you make a motion on…

Alvin Goo, Pharm D.: After considering the evidence of safety efficacy for the treatment of…so after considering the evidence of safety efficacy for the treatment of peripheral vascular disease…

Man: It should be stroke and TIA.

Alvin Goo, Pharm D.: I move that extended Dipyridamole aspirin combination is safe and effective…and efficacious. Sorry. And that aspirin and extended release Dipyridamole is not subject to therapeutic interchange.

Woman: [inaudible]

Alvin Goo, Pharm D.: I think it should just be deleted.

Woman: Okay. You did say, "Cannot be," correct?

Man: Correct.

Carol Cordy, M.D.: Okay. Is there any need for clarification?

Man: Let's read it out loud.

Woman: After considering the evidence of safety efficacy in special populations for the treatment of stroke and transient ischemic attack I move that extended release Dipyridamole aspirin is safe and efficacious. ERD/ASA cannot be subject to therapeutic interchange in the Washington preferred drug list for the treatment of stroke and transient ischemic attack. Is there a second?

Robert Bray, M.D.: Second. Dr. Bray.

Carol Cordy, M.D.: All in favor?

Group: I

Carol Cordy, M.D.: Opposed? Okay, the motion is passed.

Jeff Graham, M.D.: This is Jeff Graham. We are scheduled for break now. Which I think it will be an extended one and we have an 11:00 appointment with someone coming on the line for Statins. Is that right?

Carol Cordy, M.D.: We can't start early.

Jeff Graham, M.D.: Well, we can if I can track them down, but they are scheduled for 11:00. Let me see if I can try for 10:45. Okay?

Carol Cordy, M.D.: Okay. So we'll break until 10:45.

[break]

Carol Cordy, M.D.: Next on the agenda we have an update on the Statins and Susan Carson, are you there?

Susan Carson: I'm here.

Carol Cordy, M.D.: Would you like to start?

Susan Carson: Sure. This is the third update for the Statins report and I am presenting on behalf of Dr. Mark Helfand who was unable to attend the meeting today. In general, new evidence added this update does not change the overall conclusions of the report. The report has been peer reviewed and we responded to public comments. You will note that we made some changes to the organization of the report based on suggestions received in peer review. For example, we discussed safety in the general population separately from safety in special populations. Other changes include adding information on the baseline risk in placebo-controlled trials in Table 5.

The next slide we reviewed six Statins as in previous versions of the report. There were no new drugs added this update and the scope and key questions of the report did not change.

Slide three shows key question 1A, which asked are there doses for each Statins that produced similar percent reduction in LDLC between Satins. For this update we included a total of 60 head-to-head trials of LDL lowering, 7 new trials were added to this update and they did not change the previous conclusions, which were that the results of the head-to-head trials were generally consistent with information from the manufacturer. The exceptions were trials that were poorly controlled or reported. When Statins are provided in doses approximately equal potent a similar percent reduction in LDLC can be achieved.

Next slide. Key question 1B was, "Do Statins differ in the ability to achieve NCEP program goals?" And we've added information on new ATP goals, which include an LDLC goal of less than 70 in patients at high risk as a therapeutic option.

The next slide shows our summary for question 1B. And for this update, based on our review, we concluded that in patients who require LDLC reductions of up to 35% to meet their goal any of the Statins are effective. In patients requiring reductions of 35 to 50% to meet their goals, Atorva 20 or higher, Lovastatin 80, Rosuvastatin 10 mg or higher, and Simvastatin 20 mg or more are likely to meet their goal. We also look specifically at high potency Statins and found that Atorvastatin 80 mg daily and Rosuva 20 mg or more reduced LDLC by 50% or more. Atorvastatin 80 mg had a higher rate of some adverse events, GI disturbances and transaminase elevation then Simvastatin 80 in a trial, but in that trial the LDL lowering of Atorvastatin was greater than Simvastatin. The adverse events in withdrawal rates in patients using Rosuvastatin 40 mg were similar to patients using Atorva 80 mg in short-term trials.

The next slide reviews key question 2; How do Statins compare in their ability to raise HDL cholesterol? And in this update we reviewed a total of 57 head-to-head trials. 7 new trials that we added did not change the previous conclusions. When doses are approximately equivalent similar percent increases are achieved.

The next slide. Key question 3 was how do Statins compare in their ability to reduce the risk of non-fatal MI? CHD, CHD mortality all cause mortality, stroke or need for revascularization.

Now we are on slide 8, which shows the logic. This is from previous reports that higher LDLC reductions may be more effective, but higher Statin doses do cause more adverse events. Therefore, long-term outcome trials should be emphasized over extrapolation.

The next slide. Well, the next few slides present results of placebo controlled trials that have already been reviewed in previous versions of the Statins report. So I'm only going to mention the new trials included in this update. First, the Greece ALLIANCE and treating to new targets trials didn't meet inclusion criteria for our efficacy analysis, but they did provide information about safety of high dose Atorvastatin and they're discussed in the report under key question 4, Safety. The cards trial was added this update and I don't think these are shown on your slides. So in the cards trial Atorva 10 mg for primary prevention of cardiovascular disease was studied in patients with Type II diabetes, but who did not have elevated cholesterol levels. Patients had no history of cardiovascular disease, but they had at least one risk factor such as smoking or hypertension. In 3.9 years of follow up there was a significant reduction in cardiovascular events. The reduction in all cause of mortality was not significant. And the average reduction in LDLC was 40%. The other new trial we added was the PREVEND trial. It was a trial in the Netherlands of patients with persistent microalbuminuria and patients were randomized to Fosinopril or Pravastatin and in the Pravastatin 10 mg versus placebo arm there was no reduction in cardiovascular events after 46 months of follow up.

Now we can skip to slide No. 16, which shows two new trials that we added in inpatients with acute coronary syndrome. The other trials I just discussed were in outpatients. The first trial is Phase Z of the A-Z trial, which compared early intensive Statin treatment, Simvastatin 40 mg for 30 days and then Simvastatin 80 mg versus a less aggressive strategy – placebo for four months and then Simvastatin 20 mg. There was 24 months of follow up and despite greater lowering of LDL in the early intensive group there were no differences between the two groups on the primary end point or in any individual component of the primary outcome.

Carol Cordy, M.D.: Susan, I think we got off on the slides. Can we get back to the…

Susan Carson: I'm sorry. I can't…it's a little difficult to…

Carol Cordy, M.D.: We're not sure which slides you're on.

Susan Carson: Oh, I'm on slide number 16, and the heading is Key Question 3 – Acute Coronary Syndrome Placebo Controlled Trials continued and it's the A-Z trial.

Jeff Graham, M.D.: We don't have that slide, Susan.

Susan Carson: Those should be the ones that you downloaded from the Commotive site. I was under the impression that they were…

Woman: Is this key question 2 or 3?

Susan Carson: Three. And it should be number 16.

Jeff Graham, M.D.: Our slides are not numbered and I think this is what Barbara Ray sent us most recently. So I'm not sure we have the same slide presentation that you're giving us.

Susan Carson: I apologize for that. I was under the impression that they were sent to the center and that those were the ones that you were using. I guess I'll have to send those to you later if that would help.

T. Vyn Reese, M.D.: Could you just review the slide? This is Dr. Reese. Just go ahead and tell us what the slide said and we'll do our best to interpret.

Susan Carson : I couldn't hear that.

T. Vyn Reese, M.D.: Could you just review the slide even though we can't see it. Just tell us what it says. That would be nice.

Susan Carson: Okay. So the slide was describing Phase Z of the A-Z trial. So they found, although there was greater lowering of LDL in the early intensive group, there was no effect on the primary outcome. But several factors might explain this lack of effect. One is the early intensive group started with only 40 mg of Simvastatin and did not increase to 80 mg until 30 days after that. And patients who were taking Statins at the time of their MI were excluded. The study authors report that the trial had less statistical power than they had originally planned due to a lower than expected number of end points and a higher than expected rate of study drug discontinuation.

The second new trial that we included in patients with acute coronary syndrome was the Pact Trial, and it assessed outcomes at 30 days in patients with acute MI or unstable angina assigned to either Pravastatin 20 to 40 mg or placebo. The primary end point was a composite of death, recurrence of MI, or readmission to the hospital for unstable angina. There was no significant reduction in the primary end point or on any individual component of the primary end point in this trial.

I know you don't have the slide, but the next slide shows a summary. For key question 3 it's a table. Do you have that?

Carol Cordy, M.D.: No.

Susan Carson: No, okay. I'm sorry. It summarizes the results of the placebo-controlled trials for key question 3 by outcome and by patient population. So for all cause of mortality in patients who have never had CHD Pravastatin and Simvastatin have evidence for risk reduction. And in patients with CHD Atorvastatin, Pravastatin and Simvastatin have evidence. For the outcome of cardiovascular mortality Pravastatin and Simvastatin have evidence in patients who have never had CHD. Simvastatin, Pravastatin and Atorvastatin have evidence in patients with CHD. For the outcome of CHD events in patients who have never had CHD Atorvastatin, Lovastatin, Pravastatin and Simvastatin have evidence. And in patients with CHD Atorva, Simva, Prava have evidence. And in patients after PTCA Fluvastatin and Pravastatin have evidence.

The next slide shows key question 4. Are there differences in efficacy or safety of Statins in different demographic groups based on age, sex or race? And the conclusions for key question 4 have not changed. There is no evidence to suggest an advantage for any Statin in any demographic sub group. This update we added a pharmacokinetic study of Rosuvastatin that was conducted in the U.S. and demonstrated that…it demonstrated a two-fold elevation in median exposure of Rosuvastatin in Asian subjects. And the Rosuvastatin label has been revised to note that this increase should be considered when making Rosuvastatin dosing decisions for Asian patients.

Key question 5A – Are there differences in the safety of Statins in the general population? We concluded that there is insufficient evidence to determine which Statin or Statins are safer with regard to muscle toxicity or elevated liver enzymes in the general population.

Key question 5B now states, "Are there differences in the safety of Statins in special populations?" First, in patients with diabetes there are good efficacy data. And studies that included people with diabetes had average overall rates of adverse effects. In patients with HIV and in transplant patients Atorvastatin, Lovastatin and Simvastatin have the greatest potential for clinically important interactions. Fluvastatin has a potential for interaction with drugs inhibiting CYP2C9. And Pravastatin has the lowest potential for drug interactions and is the safest choice in those patients receiving potent CYP inhibitors.

Under drug interactions, and none of this information is new this update, the combination of antistatic with fibrates, and to a lesser extent Niacin, can result in a higher risk for myopathy or rhabdomyolosis. And that concludes the presentation.

Carol Cordy, M.D.: Thank you.

Susan Carson: Thank you.

Jeff Graham, M.D.: Susan, I wanted to make clear…I think on our slides Rosuvastatin was not listed as being included in the study, but I believe…

Susan Carson: Yeah, you must have an earlier version of the slides and I apologize for that, but Rosuvastatin was definitely included.

Jeff Graham, M.D.: Yeah, thank you.

T. Vyn Reese, M.D.: This is Dr. Reese. And Rosuvastatin still doesn't have any outcome studies. Is that correct?

Susan Carson: That's correct.

Robert Bray, M.D.: This is Dr. Bray. One of the things that we were looking at previously with the Statins was there was…the FDA had asked for additional information regarding Rosuvastatin and proteinuria and I didn't see any comments about any further information about that in the update. Do you have any information about that?

Susan Carson: No, I don't believe we've added more information about that. I'm just going to take a quick look, but I'm not aware of any specific Rosuvastatin information that we added this update.

Carol Cordy, M.D.: Are there any more questions or comments from the committee? We have six stakeholders who would like to speak. Dr. Kelley Branch. And if you all could try and limit your comments to three minutes. Thank you.

Kelley Branch, M.D.: I don't think that will be a problem. I'm Dr. Kelley Branch from the University of Washington.

Susan Carson: Excuse me. Could everyone just try to speak up a bit? I'm having a real hard time hearing.

Jeff Graham, M.D.: Yeah, make sure you speak right into the microphone.

Kelley Branch, M.D.: Not a problem. I'm Dr. Kelley Branch from the University of Washington. Fortunately, we've already had a fairly comprehensive review of the Statins, as well as some of the newer studies that have come out as far as Statin therapy. Just to underline what really is becoming more profound and was really highlighted by some of the new recommendations coming out of…published by Steve Gundry in July talking about that lower is really better and however we get there is somewhat trivial in that we really need to be pushing our patients to lower LDL's, especially those at the highest risk. In general, at least for my practice, I generally use very high dose Statins. Since I am a cardiologist my patients that are coming in are generally secondary prevention and because of that I'm using very aggressive therapies in order to get them to their goals. I generally use really the highest dose Statins in order to get them down to goal and treat them very aggressively looking at…and as you look at the curves, and I'm sure that everyone is well aware of this, as you look at the curves for secondary prevention and lesser so for primary prevention, the lower you go the less events they do have. Therefore, I try to be very aggressive and it sounds like the committee here has been rather forthcoming in looking at these high potency, as well as high dose Statins looking and balancing safety.

In my practice I generally use quite a bit of Lipitor. I also use Crestor by Toren preferentially over the other Statins just because of their efficacy and getting my patients down to the lowest possible LDL and maximizing HDL with combination therapy when needed usually with a Diason. Because of this I would like to keep my patients on these high dose Statins and it sounds like

[inaudible] the committee that that is really what is going to be done here. Because of that I really don't have much more to add at least at this point.

Carol Cordy, M.D.: Thank you. Dr. Ashley Jefferson.

Ashley Jefferson, M.D.: Hi there. I'm Ashley Jefferson. I'm also from the University of Washington. I'm a nephrologist. I look after patients with kidney disease. Patients with kidney disease have a very high risk of cardiovascular disease. At the University we also have a large Medicare population and one particular group that is at very high risk is the transplant population and I just want to comment on the use of Statins in transplant patients. Although Pravastatin has fewer interactions with the [inaudible] press of medications that we use. The majority of physicians at the University of Washington use Lipitor as their primary Statin, essentially because of the experience that we have with it. We have a long experience using Lipitor. We are aware of how to adjust the doses of Lipitor in patients who have transplants. So from that practice we would be reluctant to have to switch these patients to other Statins because of the potential for side effects in this high-risk group.

Carol Cordy, M.D.: Thank you.

Jeff Graham, M.D.: This is Jeff Graham. One thing I forgot to mention. Please identify if you're being sponsored by any organization.

Carol Cordy, M.D.: Dr. Edward Gill.

Edward Gill, M.D.: Yes, can everyone hear me fine?

Susan Carson: I can barely hear you.

Edward Gill, M.D.: Is this better?

Susan Carson: That's much better, thank you.

Edward Gill, M.D.: All right. I removed the mike from the microphone stand. It's obviously better. So I'm Edward Gill. I'm a cardiologist at Harborview Medical Center, part of the University of Washington system. I'm not sponsored by anyone, but I am a consultant for Pfizer. I am an advocate for all Statins for sure. As a cardiologist, though, I did speak at this meeting last year as well and rather than bore you with the same reiterations that I had last year, I'll just emphasize a couple of points that are worth mentioning since last year. The biggest trial that has come to date in terms of a change in thinking is the TNT trial since last year that was mentioned in the presentation. That is a trial, as was emphasized, is a trial that used intensive Statin therapy, particularly Lipitor, a dose of 80 mg, shooting for LDL levels of 70. And that was in a population of patients who had coronary artery disease. Now I also want to emphasize that again as a cardiologist we use Statins in the setting of acute coronary syndromes. That is an off label use of the Statins so I want to point that out, but clearly of the Statins out there Atorvastatin is the Statin that has the most evidence for use in acute coronary syndromes and so I just want to emphasize that. Really that's all the information that I have to add. Thank you.

Carol Cordy, M.D.: Thank you. Kris Norenberg.

Kris Norenberg, M.D.: Thank you. I'm Dr. Kris Norenberg representing AstraZeneca Pharmaceuticals. I would like to commend the committee for their recent role in implementing the Senate bill 6088. We feel that evidence-based medicine is certainly important and a benefit to all of the patients here in Washington. We also understand that this committee has been asked to review direct evidence. If it is available at the time of review that addresses health outcomes rather than intermediate outcomes. AstraZeneca believes we have a compelling list of intermediate outcomes concerning Crestor. We have long-term morbidity and mortality studies that are underway. However, they take a long time to complete. They are not yet completed. But the proof of principle has been established not only in other studies using Statins, but also studies using non Statins that show that the importance is lowering LDL, getting them to the goals set forth in the NCEP's ATP3 guidelines. We have no reason to believe that Crestor will behave any differently than any of these other LDL lowering therapies. AstraZeneca also believes that objectively reviewing these intermediate outcome data does not in any way conflict with evidence-based medicine. Regarding the safety of Crestor, in a 36-page document reviewing the safety of Crestor the FDA has found that the adverse events are no different with Crestor than any of the other Statins. Similarly there may be an added benefit that Crestor is not metabolized in the same way as many of the other Statins and therefore there is a possibility for fewer adverse events and fewer drug interactions.

We feel that the following are a testament to the medical community's acceptance of the safety of Crestor. That Crestor is currently available on 36 state Medicaid formularies. Many of those use the OHSU EPC to make their decisions. Alaska and Ohio are two in the Northwest that have added Crestor to their formularies. Crestor is also on formularies Regence, Premera and the University

of Washington. Currently 30 million prescriptions have been written worldwide in over 5 million patients. We feel that Crestor is the most efficacious Statin on a per milligram dose. The stellar trial that we performed shows that and that information is in our packaging insert. AstraZeneca also believes the state will save time and money by reducing the need to titrate Statin doses. In our study Crestor brought 80% of patients to their LDL goal at the starting dose and in high-risk patients needing to go lower than 100 mg per deciliter 50% of the patients reached that goal with the starting dose, which is greater than that for any other Statin. So just in conclusion we would like to thank you for your consideration and I ask the committee to consider the safety and effectiveness of Crestor in getting patients to goal and hope you will agree that the most effective Statins should be available to your patients who require lowering their risk of cardiovascular events and by considering Crestor for the PDL you may be saving the State considerable amounts of money without compromising patient care. Thank you.

Carol Cordy, M.D.: Thank you. Dr. Roy Palmer.

Roy Palmer, M.D.: Hello. Thank you for the opportunity to speak with you today. My name is Dr. Roy Palmer. I am a part of the medical team with Pfizer and I just want to emphasize a couple of points for your consideration. Really as regards to Lipitor we believe there are two distinct advantages Lipitor has, and that is firstly the demonstration of efficacy. And when I talk about efficacy I mean not just LDL efficacy. We know it's great at lowering LDL, we also know that it is great at reducing cardiovascular events and that's been proven by significant large clinical studies which have been presented over the last few years. In addition to that I'd like to emphasize the safety and not just safety in 12 week short studies, but we've demonstrated safety in large numbers, tens of thousands of patients treated over multiple years, 5 years, 3.3 years, 3.9 years and at…including data presented at the ACC meeting, the TNT study at the maximum 80 mg dose. I should emphasize in the TNT study 5,000 patients were treated with 80 mg and the incidence of adverse events was only slightly greater than in the 10 mg treatment arm. So it was basically because of the clinical data around Lipitor that the NCEP committee chose to recommend an optional lower LDL target and that was based upon the prove it, cards and ascot data that we presented.

So just to emphasize while we have Oregon on the phone, I would like to emphasize the importance of the TNT trial. We don't understand why the trial wasn't included in the Oregon report. It was a 10,000 patient study presented at an ACC meeting as a late-breaking study and simultaneously published in the New England Journal and I believe it should be an important part of your consideration.

So in terms of safety we have the TNT study with 10,000…5,000 patients treated at 80 mg. We have the prove it study, the acute coronary syndrome, the 2,000 patients I believe treated at 80 mg and so we know the safety over long periods of time. We don't know that from any of the other agents, but we've demonstrated that with Atorvastatin.

So to summarize, last time you reviewed the Statin class based upon the evidence of efficacy and safety you chose to recommend Lipitor as a preferred drug. We believe we present significant new data with the TNT results since your last review and we haven't seen any new outcomes data for any of the other agents apart from the A-Z study, which was a neutral study. So I would like to ask you to follow up on your recommendation last time and name Lipitor as a preferred agent. Thank you.

Carol Cordy, M.D.: Thank you. Dr. Lubber.

Lubber, M.D.: Thank you very much. I appreciate the opportunity to speak. I have been in the practice of cardiothoracic surgery for 23 years after 10 years of residency training. I was a slow learner. I spent the last 10 years both in clinical surgery and in disease management with an emphasis on lipids, hypertension and diabetes. Most of my career I've spent in academic medicine. I was last Chair at Cardiac Surgery at Albany Medical College in Albany, NY and have been back out here in the Puget Sound since 1998 as the Director of Cardiovascular Surgical Services at the Franciscan Health System down in Tacoma and I currently serve as the Chair of the Research Center Advisory Committee.

There are four components that I believe are important when evaluating current optimal drug therapy for cardiovascular disease and lipid control. Obviously the ability to achieve the lipid goals established by the NCEP and the ATP3 panel and its revised recommendations for both the LDL and HDL. The comparison of efficacy across the group of drugs currently available on the market, the evaluation of the three core components of Statins safety and muscle related adverse events, liver related events and renal function, and the cost-effectiveness assessed by dollars per milligram, decrement and LDL and incremental increase in HDL.

Addressing the first I would like to point out that dating from the first systematic review of 12,400 patients in AstraZeneca's submission to the FDA, 78% of the patients reached NCEP goals with doses of 20 mg or less and additionally I think you'll find, as I did, that 82% of all of those patients achieved the level of 100 mg per deciliter with the 10 mg dose. That data is available in the American Journal of Cardiology in 2004. Additionally, I think that it has consistently demonstrated superiority in raising APO A1 and HDL, raising it by almost a mean of 9% in all the published studies as opposed to 6% in the lower doses of other Statins and even lower levels of improvement with the higher doses of 80 mg of Atorvastatin.

Addressing the second issue I think virtually all the trials that have been conducted when comparing the intermediate LDL lowering and HDL raising of Crestor indicates a superior goal reaching ability. Specifically it takes 80 mg of both Simvastatin and Atorvastatin to achieve anywhere near the 70% goal of LDL less than 70 in the high risk population or 100 mg per deciliter in the risk population in general. I believe those doses have unacceptable side effects and cost implications. Additionally, in the most recently published review of this drug, the Uranus trial with comparing Atorva and Rosuvastatin in the diabetic population, I think you see a significant demonstration of benefit in LDL lowering and APO A1 increases and a point in fact 89% of the diabetics reached their goal with less than 20 mg of Rosuvastatin while only 74% of the Atorva group reached the goal with 20 mg and only 54% reached goal with the lowest dose of 10 mg as opposed to 75% with the 10 mg dose of Rosuvastatin.

In number three while some concern has recently…

Jeff Graham, M.D.: Excuse me, Dr. Lubber, I'm going to have to ask you to finish as soon as possible, wrap up.

Lubber, M.D.: Additionally, I think the adverse events have been effectively addressed in Crestor with placebo compared to other Statins being the same and all fell below the level of high dose Atorva and Simvastatin and indeed the renal issue was described as being not an importance issue at 96 weeks following the patients and their baseline creatinines were actually lower.

I think finally the issue of a hydrophilic Statin that has metabolized through the 2A pathway instead of 3A4 is a very important concern with new drugs reaching the market. 50% of our drugs are metabolized through the 3A4 pathway and the potential for drug interaction in those drugs metabolized there I think is considerable. And I think you need to look very carefully at the outcome data.

Jeff Graham, M.D.: We're going to have to ask you to wrap up. Also, you didn't state whether you're sponsored by…

Lubber, M.D.: No, I'm not sponsored by any company.

Carol Cordy, M.D.: Thank you. Any comments or questions from the committee?

Susan Carson: There was a question about the TNT study not being included and that study didn't meet inclusion criteria for efficacy because it compared Atorvastatin at a higher dose to Atorva 10 mg and it didn't provide the comparative information across Statins, but we did discuss it under the safety section of the report. It's similar to the Greece and ALLIANCE trials, which were also excluded from the efficacy analysis for the same reason.

Man: Can I ask the gentlemen who is sitting in the aisle to move over a little bit. I can't see the slide. Sorry, you're sitting right in front of my viewpoint here.

Susan Carson: I didn't hear that. I don't know if it was addressed to me.

Man: No, no. It wasn't addressed to you.

Susan Carson: Okay.

Man: It was addressed to the person sitting in front of the projector.

Jeff Graham, M.D.: This is Jeff Graham. Do we have any other further questions for Susan? Susan, I have one for you. We may be running a little ahead of schedule. Do you think you could come on earlier for the ACE Inhibitors?

Susan Carson: Sure.

Jeff Graham, M.D.: About maybe 12:45?

Susan Carson: 12:45? Yeah, that would be great. Talk to you then.

Jeff Graham, M.D.: Thank you.

T. Vyn Reese, M.D.: This is Dr. Reese. I don't see much in the way of new evidence. I don't see… The thing I've been waiting for Rosuvastatin, which is outcomes data, which I still haven't seen yet and I'm very cautious about that given what some of the other

Statins in the past…what's happened with them. So I don't see a reason to change our last recommendations to the State. Anybody else have thoughts about adding another Statin or changing our recommendations in any way?

Robert Bray, M.D.: This is Bob Bray. I guess I have one question for the committee, which is we have some safety data on Rosuvastatin, which we haven't mentioned, but if that comes up there was the issue about the higher levels in Asian populations. So if we do change it I think we have to be sure that we address that issue too.

Angelo Ballasiotes, Pharm D.: This is Angelo Ballasiotes. It seems that the risk of adverse events is not any greater with any of the other Statins. I guess I can't see why Rosuvastatin is not included in our list as preferred. Anybody else have any comments on that?

T. Vyn Reese, M.D.: My comment is there is no outcome data on it and we don't…there is outcomes data on the other Statins that we are looking at that we have already approved. That's my concern. I think it has a lot of advantages and if there were outcomes data on it I think I would be in favor of adding a new [end of Side A]

[Side B]

Jason Iltz, Pharm D.: This is Jason. I think we have to be clear on what we mean by outcomes, as well. I mean the target here is LDL cholesterol mainly and other surrogate markers that I think that some of the Statins may be…paint a clear picture in how well they affect those, but I don't think across the board we can say that the ones up there paint an extremely clear picture. Some are a little more murky from that regard, as well. Some are also approved for primary prevention and some are secondary prevention. So there are Statins on the board that also we don't have outcomes data for in terms of a secondary prevention, as well, but yet they are used interchangeably based on a class effect. The other thing…I agree with Angelo in that I don't know that there is something in this report that would exclude us to include it at least in the initial statement as being safe and efficacious. And I think there are some advantages to more potent Statins that we've clearly talked about. I mean any time we can use a smaller dose to get the clinical effect we want that's extremely important in lowering side effects and myotoxicity in particular with these agents. It's pretty clear that every time we double the dose of a Statin we double the risk of myotoxicity and elevation of LFT's. So any time we can achieve numbers where we can get, you know, greater than 50% or even more to goal with lower dosages I think that is preferred and being able to do that is really important with lower dosages.

T. Vyn Reese, M.D.: Excuse me, this is Dr. Reese. But remember Baycol. It had a tiny dose and it was very effective at lowering LDL's, but it also had myotoxicity. So it's not just the dose, it's the efficacy and also…by outcomes data I'm talking about outcomes…not intermediate outcomes, LDL lowering, but outcomes primary and secondary prevention. That's what I'm speaking to.

Robert Bray, M.D.: This is Bob Bray. I think my way of looking at the safety data is that even though in any one drug higher doses increase those risks I don't think we have good evidence to say that a lower dose of a high potency drug is more safe than a higher dose of a mid potency drug because I don't think there is that comparative data. So we kind of extrapolate a little bit the safety issues. My recollection from the previous recommendation was that at least some of our concerns on the safety with Rosuvastatin were the issue about the excess proteinuria that was seen in Rosuvastatin versus the other Statins and in the intervening time we have no bad outcome information associated data, but we have no other information regarding what that might mean. I know the FDA asked for more information about that, but I don't recall…I haven't seen anything about any further information. So, over time, the lack of that outcome seems to be increasingly reassuring, but I don't know that that equates the same safety as other drugs that have been out there longer.

Man: Any other comments about that?

Angelo Ballasiotes, Pharm D.: Angelo Ballasiotes again. Is there a safety issue with this drug? I guess that's my concern. If there is a safety issue then it should not be added to the formula. If there is no safety issue then it should be.

Robert Bray, M.D.: I hear what you're saying and I'm not really arguing against you as much as I think the problem is there have been some questions related to the drug that haven't been answered. I would agree with you that that doesn't equate to a known safety problem and I think that's my personal struggle with it is that we know there are some issues out there. We don't know the importance of them and the question about the importance hasn't been answered, I guess, in my review. I think our other strategy last time, which I think is still a good one is to identify which of these drugs have some uniqueness to them and try to make sure that the PDL reflects that. And so, you know, our strategy was making sure a high potency agent was on the PDL and making sure that Pravastatin, because of the relatively low degree of drug interactions, was also important to have on there. So I think that we should continue with that strategy and then I guess we have a decision to make about whether or not we want to include Rosuvastatin as part of that high potency consideration.

Carol Cordy, M.D.: This is Carol Cordy. I just wanted to clarify again, Rosuvastatin is not on the PDL in any form or where is that?

Woman: It's a non-preferred drug. So an endorsing prescriber can write DAW and get Crestor.

Carol Cordy, M.D.: Okay. Just to clarify that it is available to DSHS patients.

Donna Marshall, Pharm D.: This is Donna Marshall. How you have this motion that you made at the last meeting Crestor was not even up for consideration as being on the preferred drug list and it can't be interchanged as well because you didn't state it here. So I think…if what you are discussing is whether or not you want to include it so that if there is a non-endor…an endorsing provider that signs "may substitute at this point in time" we don't have it under therapeutic interchange because it was not included in your motion here.

Carol Cordy, M.D.: I understand that, but it is on the preferred drug list it's just not a preferred drug on the preferred drug list.

Donna Marshall, Pharm D.: No. It is not considered to be part of the drug class.

Jeff Thompson, M.D.: This is Jeff Thompson. When you call it out in this fashion you really are directing us to make it a non-preferred drug when you don't mention it on here. So therefore it does not in the deliberations in staff work ever raise up to a non-preferred status because you called it out as you were directing us to make it non-preferred. So therefore endorsing a DAW they can get it, but it won't be preferred status.

Carol Cordy, M.D.: If I were sitting here I would hear two different things from you.

Donna Marshall, Pharm D.: Dr. Thompson, it is not preferred, but we cannot interchange against it.

Carol Cordy, M.D.: But it's on the list.

Donna Marshall, Pharm D.: Yeah. It's considered part of the drug class, but it is non-preferred and the way that you stated this we don't interchange against it because you told us not to.

Carol Cordy, M.D.: But I think the confusion is it's called a preferred drug list rather than a formulary and there are non-preferred drugs that are on the list.

Jeff Thompson, M.D.: Essentially what you're saying when it…there are either non-PDL, which means it is not even in consideration for 6088 processes, and that is the vernacular that we're using now, or it's either preferred or non-preferred under the preferred drug list.

Carol Cordy, M.D.: I think it is confusing.

Jeff Thompson, M.D.: But I think, to be very succinct about this as I can be, is when you basically made the statement and listed them all out and you don't list one drug we interpret that to mean that it is not…it has a non-preferred status.

Carol Cordy, M.D.: Right.

Jeff Thompson, M.D.: But it's still subject to the DAW for the endorsing providers and then again you also need to make an indication of how it relates to interchange in any discussion we have. So…

Carol Cordy, M.D.: The issue that used to come up a lot was "are these medications available to DSHS clients or to clients who use this list?" And the answer is, "yes, they are."

Jeff Thompson, M.D.: Right. And again back to the whole idea of we don't have a formulary. If they signed a federal rebate they have access to it.

Jason Iltz, Pharm D.: This is Jason again. I don't know that I can paint a clear picture on the renal data. I'm not sure anyone has the answer, but what's interesting to me at least and I think it's important to note is, you know, Rosuvastatin was the only Statin that was asked to provide renal data to the FDA upon review. None of the other Statins did that. And it was at that point when this was potentially brought up as an issue. Since that time the Stellar trial really points towards that all Statins have a mild amount of Proteinuria associated with them, but it was never known because it was never looked at. And as the one gentlemen pointed out, there was actually…when they looked at all the different Statins at the end of the time point that they looked at, there was actually a decrease in serum creatinine although probably not clinically significant, but of note that is kind of interesting. So again I don't know that I can, you know, eliminate some of those suspicions or the cloud above that, but, you know, it was one of the first ones that had to include it.

So I don't know if we know the answer for all Statins in general or what it is if it is clinically or is it, you know, at the [unclear] list or is it tubular reabsorption. I mean what is the issue and is it significant? But we do have some data in patients with diabetes who clearly have renal problems and it appears to be safe with those populations. So as we've moved forward I think the picture will be a little clearer, but I just think that is an interesting point.

Robert Bray, M.D.: Uh, This is Bob Bray. I wonder if maybe we can break a stale mate by doing something simple before we get to an actual statement and ask how many would be against…just as a straw pull…how many folks would be against listing Rosuvastatin as part of the group adding that into that first statement?

Man: Did you say against it?

Robert Bray, M.D.: Against?

Man: I would be against it.

Carol Cordy, M.D.: That's one.

Robert Bray, M.D.: Okay. So that may help us a little bit, I guess. I'm going to be wishy washy and say that I still have the concern that have been raised because I don't, as you said, Jason, I think we don't know exactly what that means and maybe we need to temper that with the fact that it is the most potent Statin and so I guess maybe somebody who is most in favor of adding it could make a motion.

Jeff Graham, M.D.: This is Jeff Graham. I would like to point out that when you did your previous work the staff did not take the issue around safety as much as outcomes and that outcome data was not…the long-term outcome data was not there for Rosuvastatin. So that was…for some reason we must have taken a different interpretation of what you said because I know you did talk about safety, but our thought was…our thinking was, "Well, they've really [inaudible] outcomes so it's not there." I just wanted to point that out.

Alvin Goo, Pharm D.: Hi, it's Alvin. Yeah, I guess I'm sort of wishy washy on this too, but if we were to use Rosuvastatin I guess it would be in the high potency category where most people would be acute coronary syndrome. And because there was some I guess one, you know, the A-Z trial showed minimal to no effect even though the absolute difference was 2% and in a lot of…in a majority of trials that would have been statistically significant. The prove it trial did show the biggest. So there are some differences, I guess, or there may or may not be some differences as far acute coronary syndrome in reducing 270. And I guess that's where I'm sort of hung up. If we were to use Rosuvastatin for just primary prevention, which I wouldn't recommend, I don't think I would have an issue, but my concern is that with the acute coronary syndrome data.

T. Vyn Reese, M.D.: I share Alvin's concern. I think the Atorvastatin has really got the outcome studies backing it for acute coronary syndrome and I would be very uncomfortable substituting Rosuvastatin for Atorvastatin as our higher potency Statin. I just don't feel the data is there and efficacy or safety and it may be a great drug, but the jury is out, I think. And that's my concern.

Donna Marshall, Pharm D.: Dr. Reese, this is Donna Marshall. The way you have it written now I understand the comment that you just made, but would you be comfortable allowing Atorvastatin to be dispensed instead of Rosuvastatin? If you added Rosuvastatin to the first statement like Jason mentioned and left the rest of it the same then when Rosuvastatin is prescribed by an endorsing provider and signs, "may substitute" the pharmacist would be allowed to dispense Lipitor in its stead where right now they are not able to do that. A prior authorization, I think, is required at Medicaid. But with UNP the Crestor just gets dispensed as written regardless of endorsing practitioner status because it's not listed in this statement.

T. Vyn Reese, M.D.: I'm not sure I totally followed that. In other words if we left it the way it is, if we added Rosuvastatin on the top line and left Atorvastatin as the high potency option on the bottom line then it would be…what would happen?

Donna Marshall, Pharm D.: Lipitor would be dispensed in place of Crestor when an endorsing practitioner signs "may substitute" on a Crestor prescription. We would not be…Crestor may or may not be on the preferred drug list. We would still probably consider it with a cost analysis, but Lipitor would be the high potency option and they would not…if Crestor was not named as a preferred drug then Lipitor would be dispensed in place of Crestor. It would not go the other way around.

T. Vyn Reese, M.D.: How would you know it was for high potency, though? That's the question.

Donna Marshall, Pharm D.: That's for the pharmacist to determine. I mean I would imagine that if there was a prescription for Crestor that they would…I don't know. That is up to the pharmacist to determine that. But…

Carol Cordy, M.D.: I think you would have to modify the statement to have that happen.

Jason Iltz, Pharm D.: This is Jason again. My intent is not to limit the use or dictate the use of any one agent. As the other gentlemen spoke I mean I think we are all probably advocates for Statins and their benefits and we want patients to have that as outcomes, but this…by putting them all on there or by excluding it we are also saying that there is something overwhelming about that in terms of safety or efficacy that is…we're excluding it. So my intent was not to force the use of any particular agent, but to create choice and if, you know, or as it is written now if we were to add Rosuvastatin to the first sentence my understanding would be from a department head standpoint that still Lipitor and Pravachol would be on the formulary, but they would also be able to, through their choosing or based on the cost analysis, add additional agents that could include another high potency if the cost analysis showed it beneficial or they could include another agent whether that be Simvastatin, Lovastatin or any of them. It just gives them the choice to include…have those two plus any others if the analysis dictates so. That's how I would interpret the statement.

Carol Cordy, M.D.: That would be correct, yes.

Patti Varley, ARNP: This is Patti Varley and I have to say as I listen to you speak that was my understanding, too. From what I've heard I can find no strong reason to not include it and I also agree that it would be nice to have more information, but we have to decide on what we have available to us as information at the present time and I also don't see where it would stand out as there are ones that stand out in the bottom. But I can't see a rationale or a reason to exclude it in the general list.

Carol Cordy, M.D.: Do you want…

T. Vyn Reese, M.D.: You know, in the spirit of compromise I could see adding it to the top list as long as Atorvastatin was still the preferred high potency option and it was guaranteed to be on the list. Okay? As the high potency option because it has got the most data by far. There is no question…it's got the evidence.

Man: Especially with the ACS. I agree completely. And if I were to make a motion…are we ready for that?

Carol Cordy, M.D.: Yes, why don't you make a motion.

Man: I would…the motion would be that essentially we insert the word Rosuvastatin at the end of the medications available as Statins or right there is fine and leave everything else the same. And then it…

Carol Cordy, M.D.: Do you want to read it?

Man: You want me to read it? After considering the evidence of safety, efficacy and special populations I move that the following Statins are safe and efficacious – Atorvastatin, Fluvastatin, Lovastatin, Pravastatin, Rosuvastatin and Simvastatin and can be subject to therapeutic interchange in the Washington PDL. The PDL must include Atorvastatin as a high potency option and the PDL must include Pravastatin as an alternative with minimal Cytochrome P450 drug interactions.

Patti Varley, ARNP: This is Patti Varley. I will second the motion.

Carol Cordy, M.D.: Any further clarification? All in favor?

Group: I

Carol Cordy, M.D.: Opposed? The motion is passed and we'll…

Man: We'll resume at 12:45.

[break]

Jeff Graham, M.D.: And Susan, this is Jeff Graham. I wanted to say that I think this is our third time we have reviewed this class so we would like for you to focus in on any specific new information.

Susan Carson: New information, yeah. Okay, I think this should be quick because there wasn't a lot of new information added to the report. So this is the second update. There were no changes to the scope or key questions for the update. We searched the literature through February 2005. We can just skip…there were no changes to the methods; no new drugs were added to this update. The included populations stayed the same and the included outcomes are the same.

So skipping to slide number 9 about hypertension the conclusions for patients with hypertension did not change with this update. All ACE inhibitors reduced blood pressure and no other outcomes were assessed in head-to-head trials and there were no clear safety differences.

We had two trials of quality of life – Captopril versus Enalapril with conflicting results.

Moving on to high cardiovascular risk in previous CVD. This is slide number 11 and we added four new trials for this update. Slide number 11 shows APRES. It was a post revascularization study of Ramipril and cardiovascular events were reduced and all cause mortality were also reduced.

On the next slide, slide 12, the other three new trials are shown. Peace, Camelot and Asuka 2004 were added to this update. Peace was a trial of Trandolapril. There was no reduced risk of cardiovascular events or all cause mortality in a lower risk population than the population in Europa. Camelot, a trial of Enalapril found a trend for reduction in events after two years, but the difference was not significant. And lastly in Asuka 2004 also a post revascularization study of l (Quinapril?). There was no difference on the individual end point cardiovascular events or mortality, but a significant reduction in the composite end point of MI stroke and all cause mortality.

So moving on to the summary for update number two the conclusions have not changed.

On slide 14 for patients with recent MI we added no new studies to this update. So our conclusions do not change.

The next slide – heart failure. Also we added no new studies. So the conclusions remain the same.

Slide number 17 – diabetic nephropathy no new trials are completed in these patients. We do mention the Dream trial, which is currently in progress, but hasn't been published yet. We will evaluate the effectiveness of Ramipril and Rosiglitazone for prevention of diabetes in patients with impaired glucose tolerance. This will be the first study of an ACE inhibitor prospectively designed to evaluate the development of diabetes as a primary outcome.

No new studies for non…patients with non diabetic nephropathy. And no new studies or information in safety and sub groups. So that concludes our presentation.

Carol Cordy, M.D.: Thank you. Any questions from the committee?

Alvin Goo, Pharm D.: Hi, it's Alvin. I guess my question is in regards to the high risk…the use of Ramipril in the high risk group. Um, we've got now more studies with Europa and Peace and they all kind of show different results and one of the theories is that the Europa and Peace had a lower rate of patients with diabetes. So my question is, "Do you have any data regarding the Hope trial as far as if you were to pull out the 38% patients with diabetes, would there be any significant difference?"

Susan Carson: So what would the outcome be in only those patients with diabetes?

Alvin Goo, Pharm D.: Without.

Susan Carson: Without diabetes. Um, I don't think that we have that in our report. That would be something that we would have to look to see if there has been any data published on that. I don't have the answer for that right now.

Alvin Goo, Pharm D.: Okay. I was wondering maybe at the next review if that could be something if you might have access to that data at this point.

Susan Carson: I'm sorry, I can't hear you.

Alvin Goo, Pharm D.: I was wondering at the next review of ACE inhibitors if that might be something you might be able to look into.

Susan Carson: Okay. I think that is a good suggestion and we'll bring that to the center, the participating organization.

Carol Cordy, M.D.: We have one stakeholder, Mr. Jerry Gomez.

Jerry Gomez: Good afternoon. My name is Jerry Gomez. I am the Director of corporate accounts for King Pharmaceuticals. I'm here on behalf of Ramipril and just to basically reinforce some of the information that has already been provided. I do have a statement

to read, but first of all I would like to clarify that I am not a medical doctor or a Pharm D. I have a MBA from the University of Texas at El Paso.

ACE inhibitors have shown more proven effectiveness in treating hypertension, renal disease and ventricular dysfunction, as well as improved survivability of after acute MI. Although Altace shares these general indications we are not advocating Altace for these wide spread conditions, but rather a more selective targeted approach employing unique indications of Altace for patients who fit the Hope and micro Hope criteria. Only Altace has been shown and indicated to reduce the risk of CV events, to reduce mortality in patients 55 years and older without left ventricular dysfunction, but known CV risks or with diabetes plus one CV risk factor. The Hope study showed that the addition of Ramipril 10 mg daily to current regimens in patients with diabetes had a reduction and combined MI outcomes of stroke, CV death of 25%. A reduction of stroke by 33%, a reduction of MI by 22%, a reduction of CV death by 37%. The Hope II, an extension of the Hope study, published in circulation 2005 gives you 7.2 years of data and continues to build a case that the effect of Ramipril reduces the risk of cardiovascular events.

Often times, attempts are made to compare results of the clinical trials with ACE inhibitors; however, a certain amount of caution should be applied in this data since there are no head-to-head trials. For example, treatment with a relative ACE inhibitor significantly reduced the primary composite outcomes of both the high risk Hope population and the low risk Europa population. Although individual end points of stroke, CV mortality and cardiac arrest were not significantly reduced. Further, the Peace trial demonstrated a neutral effect of ACE inhibitors and primary outcomes. The Peace trial results underscore the importance of selecting a dose of any ACE inhibitor that was proven to ride clinical benefits in trials directly relevant to the patients. Evidence-based medicine should guide the use of ACE inhibitors since both blood pressure reduction and vascular effects contribute through the mechanism and the benefit. Additionally, it appears that optimal doses of the ACE inhibitors must be identified.

Finally, the use of Altace has also demonstrated to be cost effective. Two articles published; Lamay, et al and Carol et al, both showed a $111.00 cost savings in non-diabetic patients and $188.00 in diabetic patients. In summary, I would like to ask that committee to continue to maintain Ramipril on the preferred drug list, but I will also encourage the use of the Hope and micro Hope criteria in patients 55 years or older. Thank you.

Carol Cordy, M.D.: Thank you. Was there another stakeholder?

Man: Do we have any other questions for Susan? Okay, I think Susan you can go do other work now. Thank you so much.

Susan Carson: Are you ready for Beta Blockers? I want to tell Kim…

Man: I think we will- we should be in about 10 minutes, probably 10 minutes.

Susan Carson: 10 minutes. Okay, thank you. Bye.

Carol Cordy, M.D.: This is Carol Cordy. I'm looking at the previous motion from over a year ago and I think as time has gone on we changed the format a bit here. So the previous motion doesn't include indications…I don't remember from a year and a half ago whether that was conscious or not conscious or we just did it differently. So we may want to just take a look at the new template and this will be a new motion I think just because the template has changed.

Man: Should I rephrase it since I made the one last year? We should just rephrase the motion. It doesn't sound like there is any new data. There's nothing new that has been presented to the committee and so the same motion that we did last year with the new format is the one I'm going to make. After considering the evidence of safety, efficacy and special populations for the treatment of…basically what we did last year was a long list. We didn't say…so it's a long list.

Carol Cordy, M.D.: I was just looking at the slides. If you look back we have hypertension without compelling indication and hypertension with compelling indications.

Man: I will just read that list. So hypertension without compelling indications, comma, hypertension with compelling indications, comma, high cardiovascular risk, post myocardial infarction…can you type that fast?

Woman: No.

Man: You want me to start again? I'll start again.

Woman: Yeah.

Man: Okay. Hypertension without compelling indications. Hypertension with compelling indications.

Woman: Can I put with and without?

Man: Yes. That's fine. That will save lines.

Carol Cordy, M.D.: Before you go on, I'm confused from these slides because there's the one that says separates these compelling indications and if you look at the next slide some of those indications are under the compelling indications. So it's a little confusing to me as to whether we're also including indications that are other than hypertension. Am I not making that clear?

Man: I think what you're saying is that hypertension with compelling indications…a lot of those are history of heart disease and heart failure and diabetes and everything else. But, I don't know, in this it's listed both separately and together. I would follow that format. There are also separate ones like post MI without hypertension, high cardiovascular risk without hypertension and diabetic nephropathy. So you can have hypertension and more of those things and you can just have one of those things.

Man: You need to put in an indication.

Janet Kelly, Pharm D.: This is Janet Kelly. I'm really kind of wondering if we want to go down this micro dissection of every single different indication. What we had in the past was working.

Man: Yeah.

Janet Kelly, Pharm D.: Come on.

Man: But our motion was pretty scant.

Janet Kelly, Pharm D.: Clear and concise is good.

Carol Cordy, M.D.: But I would argue for trying to use this format with some indication if we can make it brief, fine.

Janet Kelly, Pharm D.: Janet Kelly. I think the format is there to help us, but if it hinders us, bag it and let's…

[multiple people talking together]

Man: We need to have you speak into the mike and identify yourself. Otherwise it comes out weird on the records.

Man: Explain what you mean.

Alvin Goo, Pharm D.: Hi, this is Alvin. You can still use the same format, but remove, "for the treatment of," and just continue on. You could say, "After consideration of evidence of safety, efficacy and special populations I move that the following ACE inhibitors are safe and effective."

Man: I think all of them have indications for hypertension and there are other indications for this. I think I should just say hypertension. Okay? Simply just say hypertension. All right? That would make it nice and simple. I'm just going to make it very simple, okay? After considering the evidence of safety, efficacy and special populations for the treatment of hypertension, I move that this long list as above all of those drugs that are listed, are safe and effective.

Woman: In the past you have been changing the effective to efficacious. Do you want to keep that.

Man: Yes, efficacious.

Woman: Okay.

Man: ACE probably should be capital ACE, I mean, all three in caps. Right? You can spell it out, Angiotensin-Converting Enzyme inhibitor, but that's a little bulky. No single ACE inhibitor is associated with fewer adverse events in special populations. Again, list all the drugs in the class can be subject to therapeutic interchange in the Washington preferred drug list for the treatment of hypertension. Ramipril must be made available to patients meeting Hope study criteria. That's at the end. I think we said may, but do we mean may or must?

Woman: May.

Man: May. [end of Side B]

Jason Iltz, Pharm D.: This is Jason. Just for a point of clarification, does that last statement…sorry, the second to last statement talking about therapeutic interchange for hypertension does that handcuff us a bit? My concern is…for example if someone would prescribed this for renal protection would that not be subject to therapeutic interchange then or does it drive off of diagnosis or does it just drive off medication?

Man: Medication.

Jason Iltz, Pharm D.: Okay, off medication. So you would still be able to therapeutically interchange any of the ACE inhibitors for any indication? Is that true?

Woman: Except for Altace and Ramipril. [inaudible]

Jason Iltz, Pharm D.: Correct.

Donna Marshall, Pharm D.: This is Donna Marshall. We wouldn't have any way of identifying why these drugs are being used so they would all be interchanged for whatever reason.

Woman: Unless you write DAW as an endorser.

Siri Childs, Pharm D.: This is Siri and if you are an endorsing prescriber and write "dispense as written" then you will get that drug.

Jason Iltz, Pharm D.: Then…Jason again. Then Ramipril is subject to, what, an expedited prior auth for a specific indication by our language. Okay? So we don't have to say, "We want it EP?" Okay.

Carol Cordy, M.D.: Should Ramipril be included in that list above or just down below?

Man: It's in the one above and below.

Robert Bray, M.D.: I think what we're saying…this is Bob Bray: I think what we're saying by that is that we want to make sure Ramipril is on the list. Right? So I think it does have to be in both places.

Patti Varley, ARNP: This is Patti Varley. I'm just wanting a point of clarification about when…as you read this and then it goes on to say…

Woman: [inaudible]

Patti Varley, ARNP: Okay. That's fine, but it has to do…there's a statement about interchange for the treatment of hypertension specifically. I want to know why that is as opposed to leaving that out and just letting it be interchanged for everything. Why we're picking out hypertension in particular?

T. Vyn Reese, M.D.: Because hypertension is what they are all approved for.

Janet Kelly, Pharm D.: Yeah, but the concern…Janet Kelly. The concern that I have is okay, now we have a patient who has heart failure and not hypertension. Are we saying we can't interchange by putting that in there? And that's not the intention here, but are we doing that indirectly by having said hypertension in the first place?

Man: We have to have some disease that they are approved to treat like you have in every other thing. We have to have an indication.

Jeff Graham, M.D.: This is Jeff Graham. I think to clarify I don't believe that in a Statin we need to put in the indication. I think that we don't really have to do that and we just got it there but that doesn't have to be done. And then it either makes it look like we're limiting or we're doing a specification that we really don't want to do.

Jason Iltz, Pharm D.: This is Jason. And that's how we handled the beta-blocker last time too. We just said that they were all safe and effective and then the comment was that there were no differences in special populations for a specific treatment. Is what we did for beta-blockers? So we didn't specifically name the indications for treatment.

T. Vyn Reese, M.D.: We can delete hypertension if that's what people want.

Man: [inaudible]

T. Vyn Reese, M.D.: That's what we did before, but that's sort of out of the format as [inaudible].

Carol Cordy, M.D.: Where are you reading that?

Man: [inaudible]

Carol Cordy, M.D.: But the motions on beta blockers separate out hypertension, angina…

T. Vyn Reese, M.D.: Actually, beta-blockers is not a good example. And the one that we just did, you know, the antiplatelets drugs we actually separated out two different distinct indications because that is what the evidence showed. So that's the precedent that I was going at. So, you know, we did have an indication before. We could put hypertension and congestive heart failure, but not all of them have been [inaudible] to do that.

Robert Bray, M.D.: This is Bob Bray. I think one of the big differences though is even though we have called antiplatelets drugs they are really very different drugs not necessarily in the same class like ACE inhibitors. So I think there is a little more homogeneity in this group.

T. Vyn Reese, M.D.: That's true.

Carol Cordy, M.D.: Carol again. The last thing on Ramipril…what I'm assuming that means is that if someone wants Ramipril for a specific indication it won't be interchanged.

Man: That's correct.

Carol Cordy, M.D.: But it has to…should we say something to clarify that? It not only may be made available but it will not be interchanged.

Woman: I think the way that it is written now it indicates that it would be preferred and we don't interchange preferred drugs.

Man: And it's worked very well for what we're doing right now.

Woman: So I believe what HRSA does is they have that on expedited prior authorization. Is that correct? And then UMP leaves it as preferred.

Man: And then as a preferred drug obviously if it's written for it, it doesn't stop either as an endorsing provider or a non-endorsing provider. It worked.

Carol Cordy, M.D.: It's worked. Well, it's worked. I guess it wouldn't be evident to me that if I prescribe Ramipril it wouldn't be exchanged for something else. I'm asking what the process would be.

Man: If it's a preferred drug it's not interchanged. The system will not tell it to do a therapeutic interchange.

Jeff Thompson, M.D.: This is Jeff Thompson. Interchange only aligns exchanges non-preferred for preferred. Not for preferred for preferred.

Carol Cordy, M.D.: So Ramipril by this statement is a preferred drug?

Jeff Thompson, M.D.: Is a preferred drug and there are EPA criteria that apply and therefore interchange doesn't get involved as a preferred drug.

Carol Cordy, M.D.: And how would one know that it met the HOPE criteria?

Siri Childs, Pharm D.: We actually say- this is Siri. We actually- the criteria is listed as any history of cardiovascular disease. We kind of really open it up. We don't say specifically the HOPE criteria. And it seems to have worked well in the past. I think that when I looked at the utilization it represents 4% of our utilization.

T. Vyn Reese, M.D.: This is Dr. Reese again. The only problem I have with this is that under our new template going back to this, it has indication…the treatment of…insert indication for how we are supposed to use our template. So it does make it…this an exception to all the other classes.

Man: I think that we didn't do that on the Statins, which we just finished. So I think we're okay.

T. Vyn Reese, M.D.: Okay, good.

Woman: Can we say that the template is optional?

Duane Thurman: Actually, I'd like…this is Duane Thurman. I'd like to make really clear that the templates are just there for guidance and that you're free to do whatever you decide to do at your discretion.

T. Vyn Reese, M.D.: Okay, so that's my motion.

Robert Bray, M.D.: Seconded. Dr. Bray.

Carol Cordy, M.D.: Any more clarification? All in favor?

Group: I

Carol Cordy, M.D.: Opposed? The motion passes.

Man: And Kim, are you on the line?

Kim Peterson, M.S.: Yes. Are you ready for my presentation?

Man: I believe we are. Oh, and I wanted to mention this is about our third review of this class so we really are most interested in any new updates.

Kim Peterson, M.S.: Okay. And I will comment that I am having a great deal of trouble hearing you folks and so after I'm finished and if you have any questions just try to speak up as much as you can. Okay. So I'm going to be making comments about our second update of the beta blocker review on behalf of Mark Helfand and I'm going to be referring to the slides that are dated May 2005. Is that what you have in front of you?

Man: Yes it is, Kim.

Kim Peterson, M.S.: Great. Okay. So with regard to slides 2 through 4 there were no changes to our searching method; our scope of eligible populations, drugs, outcomes and study designs; and these details are outlined in slides 2 through 4 in our standard format so I'm not going to go over those. I'll just skip to slide 5 entitled results, which provides an overview of the included studies.

So this slide outlines the numbers…the number of included head-to-head and placebo controlled trials stratified by study design.

Man: Kim, for some reason our slide came out blank.

Kim Peterson, M.S.: Okay. Sorry about that. When you look at them online what…you're not missing much. What is there is simply a list by population of the numbers of head-to-head and placebo controlled studies and the only thing I was going to say about that is that in this update we improved the section of the report that summarizes the results from the six head-to-head studies of quality of life in patients with hypertension and also added three new publications regarding treatment of patients with heart failure. So there was…on that slide the only thing that has changed is that there is asterisks by the word hypertension and heart failure just to show that that is where the changes were made in update 2. So let's go on to the next slide and it's entitled hypertension.

So there is no new evidence regarding the comparative efficacy of beta-blockers in patients with hypertension and so we made no changes to our previous conclusions that all beta-blockers lower blood pressure. Beta-blockers are usually inferior to diuretics in reducing mortality and there are no differences between beta-blockers and quality of life for tolerability. So the only thing to note here really is that we did add full abstraction and a more detailed descriptive assessment about the six head-to-head trials of quality of life that we had only acknowledged with a few sentences in the previous report and to…for this information you can refer to pages 11 to 12 of our report and in evidence table 1, but the bottom line didn't change and that is that there is no differences in beta blockers with regard to their effects on quality of life. So I will skip over…and now I'm going to skip over slides 7 through 9, which summarize results from trials of patients with angina and those who had a recent MI because there were no new studies in these populations and we made no changes to our previous conclusions. So this takes us to slide number 10 entitled heart failure.

And slides 10 through 14 provide a very brief summary of the main findings from 8 meta analysis, 16 placebo controlled trials, and 6 head-to-head trials in patients with heart failure and these slides really only mention the landmark trials for the three beta blockers proven to reduce mortality in patients with heart failure, we did a CIBIS II trial of Bisoprolol, the Copernicus and Comet trials of Carvedilol and the Merit HF trial of the extended release formulation of Metoprolol, Metoprolol Succinate. And so you won't find any mention of any of the three trials we added in this update because they didn't add anything to those previous conclusions. So I will just make a few brief comments about the studies just for your information, but, like I said, you won't find any of this information in the slides.

So the first trial Sys 2003 was a small placebo-controlled trial of Carvedilol in only 114 dialysis patients with heart failure, which focused on ECG parameters as their primary end points, those outcomes not meeting our criteria. However, there was…all cause in mortality was measured as one of a number of secondary end points and in… Carvedilol was significantly superior to placebo. So that is consistent with what we already know about Carvedilol.

And the second trial, Fowler 2004, was simply just another Copernicus publication and it didn't provide any additional outcomes to those that we had already reported in our previous reviews.

And the third and final trial Galatius 2004 suffered from some pretty significant methodological problems and focused on intolerance only and reported similar rates with intolerance for Bisoprolol and Carvedilol. I don't have any comments that pertain to the remainder of the slides, slides 15 through 18 regarding atrial arrhythmias, migraine and the effects of beta blockers in sub groups, because there was no new evidence in this update and no new changes to our previous conclusions. So that concludes my presentation of the second update of the beta-blocker review.

Carol Cordy, M.D.: Thank you. Any questions or comments from the committee? Do we have a volunteer for a motion?

Man: We have comments from the stakeholders.

Carol Cordy, M.D.: Oh, comments from the stakeholders.

Man: [inaudible]

Carol Cordy, M.D.: I'm sorry, I'm sorry. We do have three stakeholders. The first is Dr. Long Nguyen.

Long Nguyen: Hello. My name is Long Nguyen and I'm a Pharm D representing Glaxo, Smith & Kline. I would like to thank the P&T committee members for the opportunity to participate in the public comment process for the beta-blockers, as well as the EPC for their work. There are a couple of points that I would like to point out based on the EPC report. As indicated in table two on page five of the report, Metoprolol Succinate has an FDA indication for only hypertension, chronic stabile angina and stable and symptomatic class II and III heart failure and not post MI. And the reason for this is that the FDA evaluated the merit HF sub analysis group on patients that have severe heart failure and that group was only included 139 patients who classified as class IV and the report…the FDA reported that the merit…after evaluation of the merit HF sub group concluded that Metoprolol Succinate was effective only in mild to moderate heart failure. The sub analysis indicated there is no mortality benefit in the United States with Metoprolol Succinate in heart failure patients.

In addition to that based on the FDA indicated labeling Coreg is the only beta blockers that have an indication to use in patients with post MI with left ventricular dysfunction specifically with an injection infraction of less than 40%. And this was based on the EPC report on the Capricorn trial looking at Carvedilol as the only beta-blocker to show reduced mortality not in terms of reduction in reinfarction rate in these patients, but including fatal and non-fatal MI. And this is the base and the only clinical trials the FDA approved correct for indication for post MI patients. Therefore, with this robust evidence to randomize clinical trial and not sub hoc analysis I ask the members of the P&T committee to consider putting forth a motion to maintain the current expedite approval for heart failure patients from Class I to Class IV for Carvedilol and consider adding another extradite approval for a completely separate patient

population specifically those that are post MI with left ventricular dysfunction with an injection fraction of 40% or less. With that I will be happy to take any questions that any committee members have.

Carol Cordy, M.D.: Thank you.

Long Nguyen: Thank you.

Carol Cordy, M.D.: Dr. Kris Norenberg.

Kris Norenberg, M.D.: Thank you. I'm Dr. Kris Norenberg representing AstraZeneca Pharmaceuticals. I would like to just say a few comments about Metoprolol Succinate also known as Toprol-XL. I'll just summarize. We don't disagree with anything that he said. We don't disagree with the indications for Toprol-XL. However, we would like to see it added to the PDL because it is unique amongst the once daily beta-blockers that are indicated for hypertension, angina and then the mild to moderate heart failure.

We feel that the once daily dose of Toprol-XL is advantageous in that it avoids a lot of the peaks and troughs in blood concentration; therefore delivering a more consistent level of beta block aid throughout the day. This is particularly important for heart failure patients in which the cause of mortality is often sudden death associated with arrhythmia.

Toprol-XL is the most widely prescribed brand medication by cardiologists. It is currently available in a preferred position on over 90% of managed care formularies nationally. Locally, Regence, Premera, PacifiCare of Washington and KPS Health Plans offer Toprol-XL in a preferred position. So we would simply ask that you add Toprol-XL to the PDL as an alternative from which physicians can choose for those patients with mild to moderate heart failure in which it is indicated. Thank you.

Carol Cordy, M.D.: Thank you. Any discussion from the committee?

Jeff Graham: This is Jeff Graham. Do we have any further questions of Kim? Or Kim, do you have any further comments?

Kim Peterson, M.S.: No, I don't disagree. Thank you for the public comment and I…we don't disagree with any of the comments. We did make an attempt in this update to clarify our position about the post hoc sub analysis of the Merit HF trial in patients with severe heart failure that it is indeed a weaker level of evidence…its evidence, but a weaker level. So we were hoping that that was an improvement.

Jeff Graham: Well then, Kim, thank you so much and I think that probably you've provided the information that we needed.

Kim Peterson, M.S.: Okay, great, thank you. Bye.

T. Vyn Reese, M.D.: This is Dr. Reese and looking at the beta-blocker templates before we broke them all down by indications. So we'll have to…I assume that we're going to have to do that again unless there is some other way of handling this because they all have different indications. This is more like the antiplatelets…

Donna Marshall, Pharm D.: Excuse me, Dr. Reese, this is Donna Marshall. Are you expecting to make changes to any of these?

T. Vyn Reese, M.D.: No.

Donna Marshall, Pharm D.: Because in the past you have said just to renew the previous motion.

T. Vyn Reese, M.D.: That's right.

Donna Marshall, Pharm D.: Or the previous resolution.

T. Vyn Reese, M.D.: That's what we did before but they are not in the new format.

Donna Marshall, Pharm D.: They don't have to be. You could say that…you just go with the previous decisions or just renew those decisions.

T. Vyn Reese, M.D.: Great. That would be a lot easier.

Donna Marshall, Pharm D.: And I will include the previous motion as part of your new motion just so that we have a record of what that decision was.

T. Vyn Reese, M.D.: Super.

Alvin Goo, Pharm D.: Hi, it's Alvin. I just have one comment and open up the discussion is for the indication of CHF. Um, I had thought that at the last meeting we had said that Carvedilol and Metoprolol Succinate should be on, but I only see Carvedilol. Is that…is that the committee's understanding?

Jeff Graham: When we look at your motion it listed all three of those drugs to be shown to be equally safe and efficacious. And so I don't think there was any further…well, wait a minute now.

T. Vyn Reese, M.D.: We put Carvedilol on it for preferred position for heart failure…Class IV heart failure, but that's not what it says.

Donna Marshall, Pharm D.: I don't think you made Metoprolol Succinate be on…added to the list because you also said that Bisoprolol and Metoprolol Succinate may be subject to interchange.

Alvin Goo, Pharm D.: Okay. Could I make a suggestion that we place Carvedilol and Metoprolol Succinate in that category?

Carol Cordy, M.D.: Why don't we go ahead and just make for that particular indication make another motion? Because it will change that. Just redo this…can you get to the congestive heart failure? Did you want to make a motion that that changes?

[inaudible]

Carol Cordy, M.D.: Just make it a new motion.

Alvin Goo, Pharm D.: Okay. So the motion is for congestive heart failure…the indication of congestive heart failure to say after considering the evidence of safety, efficacy and special populations for the treatment of congestive heart failure I move that Bisoprolol, Carvedilol and Metoprolol Succinate are safe and efficacious. No single beta-blockers associated with fewer adverse events in special populations. Carvedilol and Metoprolol Succinate should be on the Washington PDL for heart failure patients.

Carol Cordy, M.D.: I think it just ends after heart failure patients, period. Then the last two lines are deleted.

T. Vyn Reese, M.D.: For the indication of heart failure.

Carol Cordy, M.D.: For the indication of heart failure. Oh…period. And then delete the…delete it after heart failure.

Janet Kelly, Pharm D.: Janet Kelly. I'm kind of confused by what the…what we're trying to do with this motion. We have three drugs that we are saying are equally safe and efficacious. We initially pulled the Carvedilol out because the body of evidence is greater for that drug and now we're putting the Metoprolol extended release in there and I'm wondering…are you saying that Carvedilol and Metoprolol extended release are unique and different and that we need to have both of those options? Clearly we need something for…

Man: Yep.

Janet Kelly, Pharm D.: Okay. And where's the data for that?

Man: Well, the data is that there are placebo-controlled trials with Metoprolol Succinate and there are placebo-controlled trials with Carvedilol and there is a comparative drug trial of Carvedilol with Metoprolol Tartrate, which did show superiority with Carvedilol. The question begs is that because of its Tartrate it's not dosed appropriately. It was only BID. We know that Metoprolol should be dosed Q8. So there really wasn't a fair comparison. I guess from Carvedilol to Metoprolol Succinate. So because there is evidence that in placebo trials Carvedilol…I mean Metoprolol Succinate was superior that there leaves some room that, you know, you could use Metoprolol Succinate for mild CHF. As it stands right now I cannot prescribe Metoprolol Succinate for CHF. It gets rejected.

Woman: What about [inaudible]. That's proto. We don't have anything with that one. We put it up at the top but yet we're not addressing that.

Jeff Graham, M.D.: This is Jeff Graham. If you prescribed it and signed DAW it is available.

Man: Correct, but at least I've been sort of training my physicians to write for the substitute as permitted so that's what they are trained to do. I'm just trying to prevent just more delays and more callbacks to the office.

Jeff Graham, M.D.: So you mean if somebody wrote for Carvedilol and substitution permitted that then you would switch them? You would not?

Man: No. When a provider writes for Metoprolol Succinate and it's for CHF, which is appropriate, it gets rejected, I get a call.

Jeff Graham, M.D.: That's correct.

Woman: Unless you sign…

Jeff Graham, M.D.: Unless you sign DAW.

Man: Correct, but we're trying to train our physicians to write under the dispense as written.

Donna Marshall, Pharm D.: I think that we…this is Donna Marshall. We need to stick to the evidence and not your preferences of prescribing on making those decisions.

Man: Correct. Right. And there is evidence to support the use of Metoprolol Succinate for CHF.

Donna Marshall, Pharm D.: So then the question is, is do we need both of these on the preferred drug list or either/or?

Man: I think it would be good to have an option when there is no clear…there is no clear evidence one way or the other that one is superior than the other.

Jeff Thompson, M.D.: This is Jeff Thompson. I just want to make it very clear…you will need to be very clear about that—either/or or both.

Man: Both.

Jeff Thompson, M.D.: So both need to be on the preferred drug list as preferred status for this indication?

Man: That would be my recommendation.

Patti Varley, ARNP: And this is Patti Varley and I guess point of clarification again is when I look at that up there the language to me says that there are three drugs at the beginning that are safe and efficacious for congestive heart failure and then it says no single beta blocker is associated with fewer adverse events. Then it was two that should be on the PDL for heart failure. And so to me that's confusing as to why there are three listed and then two listed that basically say the same thing and I don't understand why that is.

Donna Marshall, Pharm D.: The way it is right now we would not…if we were to pass this motion we would not be able to interchange Bisoprolol for one of these two drugs because you have told us not to interchange it. You have not told us that it can be interchanged. So I think what you need to do is reinsert the Bisoprolol only can be interchanged. You said these two cannot be. Are you implying that the Bisoprolol can be?

Carol Cordy, M.D.: I think…this is Carol Cordy. I think we want to add it after the first heart failure and leave out that not be interchanged part. Delete the last…

T. Vyn Reese, M.D.: That means they can be interchanged then. You don't want them to be interchanged. You could use Bisoprolol for those.

Carol Cordy, M.D.: You wouldn't interchange them. You don't have to have that extra...

Jeff Thompson, M.D.: But could they be interchanged for each other? That's the question. They don't have the same indications.

Carol Cordy, M.D.: Not if they are preferred.

Donna Marshall, Pharm D.: We don't interchange the preferred drugs.

Carol Cordy, M.D.: I'd leave off patients too…just heart failure is what we…

Man: Or we could recommend…you have two…we must have two available of the three.

Man: I like your first thinking.

Donna Marshall, Pharm D.: So do we want to strike this motion and start a new one? Or no?

Man: Just leave it.

Donna Marshall, Pharm D.: Okay.

Jason Iltz, Pharm D.: This is Jason. My only concern is how do we ensure…and maybe this is at an EPA level or something like that. How do we ensure that the appropriate patients that could benefit from Carvedilol so are more severe patients receive that versus Metoprolol Succinate, which is really approved for Class I, Class II? I mean that's my concern. So the way this is set up here I guess I need to know more about the other end. And if it would stay like this do we need to specifically tell them what the criteria is for each? I mean that's my concern. Do you see where I'm going for that? I mean it's different…I know your institution is one way, but I'm looking from a general sense in an ambulatory care setting and those sorts of things, how is that end pharmacist going to know which is appropriate based on that patient?

Carol Cordy, M.D.: This is Carol Cordy. I think this has come up so many times that there is…we were talking about there are pearls that we learn about which drug to prescribe for which indication for which patient and we haven't had a good format to do that. In the past we haven't included that in this because it goes into so much detail that we assume that the prescriber and the pharmacist know what they are doing and what they are prescribing medications for. And I think if we tried to do that it needs to be in another format—an educational piece.

Duane Thurman: This is Duane Thurman. I guess one of the things that we…the reason we keep coming back to this…and I'm not a pharmacist or a doctor. So cut me off if I stop making sense, but I think what the purpose here is, is to make the drugs available in a way that allows for the practitioners dispensing authority and the pharmacists ability to interchange within the program to occur. I mean the way I read this here, is that if both of those drugs at the end are going to be available and if a prescription comes in for one or the other they will not be interchanged and so the…I think that sort of takes you about as far as you can go in terms of being prescriptive in terms of what the P & T's position should be because I would assume if I'm the practitioner I would write for one of those drugs. I would know which drug I wanted and this gives me the protection to know it won't be interchanged. If I happen to write for the wrong drug that's a different issue and I don't think that you can put into your motion and prevent. I mean there's a certain…there's just a certain amount that you can't control. You're just setting a formulary and then you're relying on people to exercise their professional judgment.

Carol Cordy, M.D.: That's what I was trying to say. You said it better.

Man: But Duane…you used the "f" word again.

Duane Thurman: No comment.

Siri Childs, Pharm D.: This is Siri. We can do whatever you want us to do. If you want it to be differentiated between Class I and II and III and IV or I, II, III and IV, or have it all be just open we can do whatever you would like us to do.

T. Vyn Reese, M.D.: This is Dr. Reese. I think we need to stop micromanaging. I think it's fine the way it is. I think you need to have…the provider some credence for, you know, a modicum of intelligence. It may not be true, but that's…we have to let the provider [inaudible] make the decision and not micromanage the whole thing.

Robert Bray, M.D.: This is Dr. Bray, you know, as someone getting the calls I prefer to get calls from pharmacists when they really have something to add to what's going on as opposed to both of us being frustrated about, well, you know, we hit a stop and we gotta do something about it. So, you know, and hopefully pharmacists will call when it has nothing to do with this and when you say, "Gee, Bray, I think you're screwing up on this patient." I hope I keep getting those calls. Not that that ever happens.

Carol Cordy, M.D.: Any other discussion? Do we have a second?

Man: I'll second it.

Carol Cordy, M.D.: All in favor?

Group: I

Carol Cordy, M.D.: Opposed? The motion passes.

Robert Bray, M.D.: Dr. Bray. The one thing I've noticed in reviewing our previous motion is that there is not listed an indication for post MI therapy and there was on our motion prior to that in 2003 and I'm wondering if that was an omission or it got left off the…it existed, but wasn't…isn't here?

[inaudible]

Duane Thurman: You know, it's just kind of a housekeeping matter. Are there certain indications where you are going to reaffirm your previous motions? It might be easier if you reassert the ones that you're not going to change and then say…and for the following ones we are either doing a new motion or we're modifying a previous motion. And if you want to consider the one that was not brought up the second time, but was brought up the first time we could incorporate that by reference also…or three of them.

Man: I'm trying to remember why we deleted that and I think it was because we had…with angina and some of the other indications we felt we had it relatively well covered and that we just decided that was going to be in addition and we didn't want to make…I can't remember why we didn't reaffirm that recent myocardial infarction. It looks like it is addressed in page three of the review. Its recent myocardial infarction…and actually it differs from the list that we had the first time. Okay? Which is they are different drugs. Acebutolol, Metoprolol Tartrate, Propranolol, Timolol and Atenolol. Those were the four that were in recent myocardial infarction. These studies were conducted before ACE inhibitors and modern interventional therapy was used. That's the other reason that the data was so old we weren't sure how it applied to current treatment of post myocardial infarction patients. So I think that's why we didn't do it again as I remember. Maybe we should just leave that as an ancient, historical footnote and go on.

Man: I think I would like to ask you to make a motion to reaffirm your motions of December 15, 2004 in migraine headaches, hypertension, angina, atrial arrhythmias and bleeding esophageal varices.

Carol Cordy, M.D.: And the only thing I would say is since we're being consistent we should now replace effective with efficacious and not have to redo these all, but just change that word in those five…

So do we need a formal motion to…?

Man: I move that we reassert our previous motions of 12/15/04 with the exception of replacing the word efficacious for effective. And that would be for migraine headaches, hypertension, angina, atrial arrhythmias and bleeding esophageal varices.

Carol Cordy, M.D.: I'll second that. All in favor?

Group: I

Carol Cordy, M.D.: Opposed? The motion passes.

Man: And you already did congestive heart failure so you're done. So I think we are scheduled for a 15-minute break while we prepare for the DUR...

Duane Thurman: I'm sorry, this is Duane Thurman. Just a point of clarification on your motion. When you say that you are reasserting the motion…the last motion, are you saying it except for the word…replacing the word effective with efficacious and also replacing the prior motion on congestive heart failure?

Man: That's correct.

Duane Thurman: So to be absolutely clear we have reasserted everything except for the congestive heart failure motion, which has changed and we will be changing the word effective to efficacious in the prior motions? Thank you.

Carol Cordy, M.D.: So we'll break for 13 minutes and be back here at 2:15. Thank you.

DUR Board Meeting Minutes
September 21, 2005

WASHINGTON STATE PHARMACY AND THERAPEUTICS COMMITTEE MEETING
Regular Meeting
Radisson Hotel SeaTac

2:00pm – 4:00pm

Council Members Attending: Alvin Goo, PharmD, Patti Varley, ARNP, Carol Cordy, MD, Robert Bray, MD, T. Vyn Reese, MD, Angelo Ballasiotes, Pharm D., Jason Iltz, Pharm D., and Janet Kelly, Pharm D.

Health and Recovery Services Administration, Division of Medical Management Coordinating Staff: Jeff Thompson, MD, DMM Chief Medical Officer; Siri Childs, Pharm D, Pharmacy Policy Manager; Nicole Nguyen, Pharm D, Clinical Staff Pharmacist

I. ADMINISTRATIVE ITEMS

The meeting was brought to order by chairperson, Carol Cordy, MD. The minutes of the previous DUR Board Meeting in June, 2005 were approved.

II. DUR: 2004-2005 Retrospective Drug Utilization Review for Washington Medicaid

- **Intensified Benefit Management Intervention Focus- October 2004 to September 2005**

Talmahjia Sweat, Pharm.D. with MAA's claims processor, Affiliated Computer Services (ACS), provided an overview of the interventions and outcomes done for MAA under the Intensified Benefit Management (IBM) program. Most of these interventions were done by fax communication with the providers. About 1000 clients were targeted per month for each intervention. After MAA determines what the intervention will be for the month, clinical collateral is developed and is then approved by MAA. These interventions promote appropriate pharmaceutical care such as targeting duplication of therapy, promote cost-effective drug therapy, and/or support the preferred drug list program. Dr. Sweat's presentation is attached.

The IBM for October 2004 targeted 115 clients (101 prescribers) receiving two or more SSRIs. There was a 25% response rate, and of these responders, 59% agreed to change therapy. There was also an educational program in October directed at 390 pharmacies filling fluoxetine 40mg prescriptions for 810 clients. This program required no response and was to inform them that a cost-effective option for MAA is the filling of two 20mg capsules a day instead of one 40mg capsule a day.

The IBM in November 2004 targeted 1108 clients (546 prescribers) on a non-preferred estrogen to promote the use of the preferred estrogens. There was a 53% response rate, and 67% of those who responded agreed to change to a preferred estrogen. This same intervention was done in December 2004 targeted at 1104 clients (591 prescribers) on non-preferred estrogens. There was a 58% response rate and 87% of the responders agreed to change to a preferred estrogen.

In January 2005 the IBM focused on 1065 clients (325 prescribers) who were using non-preferred insulin-release stimulant type oral hypoglycemics. 53% of prescribers responded, and 78% of these responders agreed to change to a preferred drug.

The IBMs for February, March and April 2005 targeted clients receiving two or more of the second generation antidepressants (SSRIs, mirtazapine, nefazodone, bupropion, duloxetine and venlafaxine). In February 1016 clients were targeted (739 prescribers), in March 1007 clients were targeted (663 prescribers), and in April 618 clients were targeted (484 prescribers). A survey was sent out to the prescribers to find out why they chose the combination of second generation antidepressants.

Another intervention was done in April 2005 targeting 437 patients (347 prescribers) on COX-II inhibitors. Prescribers were requested to review the patient's use of the COX-II inhibitor and the patients cardiovascular risk as a result of the FDA warnings. 44% of prescribers responded, and of these 37% discontinued therapy.

In May 2005 the IBM focused on 1017 clients (798 prescribers) receiving a non-preferred second generation antidepressant. There was a response rate of 40%. 53% of the responders continued with current therapy, 14% planned to modify therapy and 2% discontinued therapy.

The June IBM targeted clients who received a schedule II or III narcotic and had greater than 10 narcotic prescriptions in a month, or greater than 7 narcotic prescriptions in a month for 6 months within a 12 month period. All cancer and hospice clients were excluded. There were 106 clients, and 878 different prescribers. Of the 17% who responded, 33% no longer saw the client, 23% had never seen the client, 11% thought therapy was appropriate, 7% planned to discontinue therapy, and 6% planned to modify therapy.

In July 2005 the off label use of anticonvulsants were targeted. There were 1024 clients and 876 prescribers. Results were not available at this time.

The narcotic review from June was done again in August 2005. There were 76 clients with 488 prescribers contacted. Results were not available at this time.

The off label use of anticonvulsants are planned to be done in October 2005.

- **Therapeutic Academic Service (TAS) Intervention Focus – October 2004 to September 2005**

Krista Isakson, R.Ph. with ACS provided an overview of the TAS for Medicaid. Krista is one of the pharmacists who provide face to face interventions with a total of 120 prescribers each month. These interventions address inappropriate prescribing patterns, promote cost-effective therapies, and provide education on drug therapies and client programs. These prescriber visits compliment the IBM interventions each month. An additional intervention was done in October 2004 to educate and provide a monitoring tool to identify and manage hyperglycemia risk and other adverse effects that occur with atypical anti-psychotics.

III. Narcotic Review Program

Jeff Thompson, MD, Chief Medical Officer for HRSA provided an overview of the Narcotics Review Project. This program included 320 clients with use of over 10 opioid prescriptions in a month or more

than 7 narcotic prescriptions in a month for 6 months in a year. The majority of these clients were between the ages of 35-54 years old, female, and Caucasian. HRSA was paying $7.5 million a year for these clients, which was 4 times the cost of the average Medicaid client. These clients cost $2500/month and the average Medicaid client cost $650/month. Starting in July 2005, all schedule II and III narcotic prescriptions were stopped for these clients and the prescribers were faxed to ask if these prescriptions were medically necessary, if they wanted to continue to fill the prescription, and if HRSA should continue to require prior authorization for the client's prescriptions. If the prescriber indicated that the prescription should be filled the prescription would be authorized and the pharmacy could fill the prescription. If the prescriber indicated no, the prescriber would contact the pharmacy to cancel the prescription. If the prescriber did not respond, the pharmacy could fill an emergency supply and a letter was sent to the prescriber. In the initial results 23% cancelled the prescription, 56% asked to keep the client on prior authorization, and 15% did not respond. Prescribers were thankful for the information, but there was some push back from providers with abnormal prescribing practices. These clients were also screened for eligibility for inpatient and outpatient drug treatment programs.

IV. MANUFACTURERS' PRESENTATION

None

V. STAKEHOLDERS' PRESENTATIONS

None

VI. RECOMMENDATIONS OF COUNCIL

Members of the council complimented the agency on the programs in place and agreed that they are worth continuing.

ADJOURNMENT